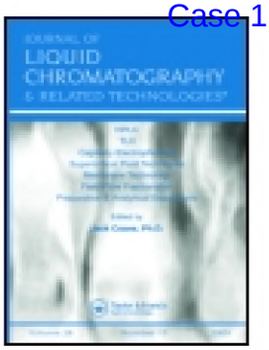
Exhibit 40



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Identification and Control of Impurities for Drug Substance Development using LC/MS and GC/MS

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Abstract: Identification and control of impurities for drug substances is a critical task in pharmaceutical process development for quality and safety. The most commonly used analytical technique for impurity analysis in drug substances and drug products is undoubtedly a chromatographic method, namely high performance liquid chromatography (HPLC). Impurity profiling is typically performed by HPLC and impurities are further tested for identification and confirmation by other techniques. Several case studies are presented in this paper to report the identification of unknown impurities employing chromatographic techniques interfaced with mass spectrometry. The task of unknown identification was facilitated by complementary methodologies including tandem mass spectrometry (MS/MS), high resolution mass spectrometry (HRMS), preparative HPLC and NMR. Upon identification of the impurity, the impurity formation was monitored and controlled throughout the synthesis. Three case studies are described where unknown process impurities were analyzed for identification using LC/MS and GC/MS methodologies. It is demonstrated that identification of the unknown impurity enabled chemists to pinpoint the chemical step of impurity generation, aiding the effort to reduce or even eliminate the impurity in the drug substances.

Keywords: Control of impurities, Drug development, GC/MS, LC/MS

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INTRODUCTION

Impurity profiling is one of the most critical analytical tasks during the development of drug substances (also known as active pharmaceutical ingredients, API). The level of impurities is tightly controlled by regulatory agencies for toxicological assessment and clinical studies. ICH guideline Q3A(R) requires that organic impurities at or above 0.1% (or 1.0 mg total daily intake, whichever is lower) should be identified for drug substance with maximum daily dose of less than 2 g/day.[1] The most established analytical method for impurity profiling is indisputably high performance liquid chromatography (HPLC) with UV detection. The organic impurities are usually determined by HPLC/UV first and further analyzed by other analytical techniques including LC/MS, MS/MS, HRMS, preparative LC, and NMR (nuclear magnetic resonance). With the advent of atmospheric pressure ionization methods such as electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) enabling a smooth transition of samples from the liquid phase (HPLC) to the gas phase (MS), LC/MS has become a prominent analytical technique for both quantitative and qualitative purposes in pharmaceutical research and development.[2]

Identification and tracking of organic impurities using LC/MS related technologies for drug substance[3–12] and drug product[13–16] development is well documented in the literature. Most of the reported cases employed multi-disciplinary approaches in order to elucidate the impurity structures, namely, tandem mass spectrometry (MS^n), high resolution mass spectrometry (HRMS), LC/UV, LC/MS, LC/NMR, NMR and preparative LC. Quadrupole-based mass spectrometers (single quadrupole and triple quadrupole MS) are by far the most widely used MS types. Single quadrupole MS can provide molecular ion information and in certain cases fragmentation data through in-source collision induced dissociation (CID). In comparison, triple quadrupole MS is useful for acquisition of MS^2 tandem mass spectral data. It has been reported that trace level impurities were identified using ion trap multistage tandem mass spectrometry followed by preparative LC for confirmation by NMR.[3,10] Ion trap-based mass spectrometry provides MS^n fragmentation pathways, compared to quadrupole-based mass spectrometry which offers MS^2 stages, rendering in-depth structural information for impurity identification.[2] High resolution mass spectral data can add another dimension to the analytical information for the determination of impurity by providing elemental compositions.[11,14,15] The combination of the multistage tandem mass spectrometry and accurate mass measurement gives an extremely powerful analytical tool, FT-ICR-MS (Fourier Transform Ion Cyclotron Resonance Mass Spectrometry). This device

is capable of providing elemental compositions of the molecular and fragment ions for the n-th order of tandem mass spectral data. Several groups reported the use of FT-ICR-MS for the identification and confirmation of unknown impurities.[8–10] The process impurities are expected to have structural similarity to the drug substance. Therefore, the mass spectral fragmentation pattern of the process impurities were compared to that of the drug substance, and impurity structures were postulated in the reports. The identity was subsequently confirmed by NMR experiments on isolated impurities, or in certain cases the postulated compound was synthesized for unequivocal confirmation.

Isolation of the impurity via column chromatography or preparative HPLC is a labor-intensive and time-consuming task, and therefore it is avoided whenever possible. However, there were reported cases where the unexpected toxicity and color of the drug substance made the fractionation of the impurity inevitable. The impurity responsible for the unexpected color of the drug substance was much less than 0.1%, but the impurity had to be identified to understand the origin of formation and to reduce or eliminate the impurity.[4] An unexpected toxic response during an animal toxicological study from a drug substance batch was observed, and the batch was fractionated to pinpoint the impurity, though the level of the impurity was lower than 0.1%.[11] In both cases, preparative HPLC was used to fractionate and enrich the impurities.

Most drug substances are too polar or thermally labile to be subject to a gas chromatographic analysis, which requires vaporization of the samples into the gas phase. However, for analysis of raw material and intermediates, gas chromatography offers several advantages including high separation efficiency, wide dynamic range, and various compatible detectors such as FID (flame ionization detection), ECD (electron capture detection), TCD (thermal conductivity detection), and MS. Especially GC/MS is a powerful analytical technique for identification of unknowns due to the availability of vast and accessible spectral libraries.

In this report, three case studies of unknown process impurities are presented. The impurities were first detected by HPLC/UV and GC/FID, and they were subject to LC/MS and GC/MS analyses to obtain molecular ion information. Further analyses such as MS/MS, HRMS, preparative HPLC, NMR, and synthesis of the authentic compound were performed to elucidate the impurity structures. The knowledge obtained helped to understand impurity formation and was used to improve the quality of the drug substances.

EXPERIMENTAL

Reagents

HPLC grade water and acetonitrile were obtained from EMD Chemicals (San Diego, CA, USA). Formic acid was purchased from Fluka (St. Louis, MO, USA), and perchloric acid was obtained from Sigma Aldrich (St. Louis, MO, USA). All reagents were used as received.

Instrumentation

Agilent (Santa Clara, CA, USA) 1100 HPLC systems with ChemStation software were employed for liquid chromatography work. A typical HPLC system consisted of a degasser, a binary pump, an autosampler, an ALS thermostat, a column compartment, and a diode array detector (DAD). GC/FID and GC/MS data were obtained using Agilent G6890N with FID (flame ionization detection) or MSD (mass selective detection) with ChemStation software. A Micromass/Waters (Milford, MA, USA) Quattro Ultima triple quadrupole mass spectrometer with MassLynx control was used for tandem mass spectrometric data generation. An ionization mode of positive electrospray was used with the following parameters: capillary voltage 3.5 kV, cone voltage 20–35 V, drying gas nitrogen, collision gas argon, and collision cell pressure 1.0×10^{-3} mbar. High resolution mass spectral data were obtained using an Agilent LC/MSD TOF mass spectrometer in a positive electrospray ionization mode with the following parameters: capillary voltage 3.0 kV, drying nitrogen gas temperature 350°C, and fragmentor 70–150 V. The samples were introduced to the mass spectrometer via flow injection without a chromatographic separation. Impurity purification by preparative LC was performed using a Shimadzu (Kyoto, Japan) system consisting of a SIL-10AP auto-injector, two LC-8A pumps, SPD-10A VP UV-VIS, SCL-10A VP system controller, and FRC-10A fraction collectors with Discovery VP software.

Case Study A

Analytical HPLC Conditions

The column used for analytical HPLC experiments was an Agilent Zorbax SB-CN 4.6 mm × 150 mm, with particle size of 3.5 um. Mobile phase *A* was water with 0.5% (v/v) perchloric acid, and mobile phase *B* was acetonitrile. The flow rate was 1.5 mL/min with the column

temperature maintained at 25°C. Gradient elution profile was to hold at 0%B for 3 min, linear gradient to 40%B at 4 min, hold at 40%B until 12 min, linear gradient to 60%B at 17 min, to 100%B at 18 min, and hold at 100%B until 20 min. The sample diluent was methanol and injection volume was 5 μL. UV detection wavelength was 220 nm. The perchloric acid used in the mobile phase was replaced with formic acid for acquisition of mass spectral data.

Preparative HPLC Conditions

For preparative purification of the impurity, a Waters XBridge Prep C18 OBD (19 mm ID × 150 mm L, with 5 μm particle size) was used. The mobile phase *A* was water and the mobile phase *B* was acetonitrile without any modifier. The use of modifier in the preparative LC was intentionally avoided whenever possible to prevent any decomposition of the collected samples, even though it meant a slight loss in the chromatographic resolution and peak shape. The acidic or basic modifier used in the LC mobile phase could become concentrated during the solvent evaporation step, and cause decomposition of the collected fractions.[5] The flow rate was 10 mL/min with a gradient elution profile from 10%B to 37%B in 20 min, and constant at 37%B until 50 minutes. The UV wavelength was at 220 nm and the column was held at an ambient temperature. The sample diluent used was methanol. The solvents were evaporated from the fractions using a rotary evaporator.

GC/FID Conditions to Monitor the Intermediate B

The GC column used was DB1701, 30 m length, 320 μm ID, with film thickness of 1.0 μm. The carrier gas was helium with a constant flow rate of 1.5 mL/min. The inlet temperature was 250°C with a split of 30:1. The oven temperature profile was to hold at 80°C for 0.5 min, to ramp to 220°C at a rate of 15°C/min, and to hold at 220°C for 1 minute. The FID temperature was 300°C.

Case Study B

A Waters XBridge C18 column (4.6 mm × 75 mm, with 2.5 μm particle size) was used and water (mobile phase *A*) and acetonitrile (mobile phase *B*) with 0.1% formic acid were employed as mobile phases. The flow rate was 2.0 mL/min with a gradient of 20%B to 90%B in 10 minutes. The column temperature was kept at 40°C.

Case Study C

The GC column was Agilent DB1701, 30 m × 0.32 mm ID, with 1 μm film thickness. Inlet temperature was at 200°C with helium as a carrier gas, constant pressure at 10 psi, and split of 25:1. The GC oven temperature profile was to hold at 35°C for 7 minutes, ramp to 80°C at 7°C/min, ramp to 180°C at 15°C/min, then hold at 180°C for 2 minutes. The FID temperature was 250°C.

Additional experimental conditions are described as needed in the Results and Discussion section for each example discussed.

RESULTS AND DISCUSSION

Case Study A

An HPLC method was developed for reaction monitoring of a fixed synthetic route for a development compound. Figure 1(a) shows an

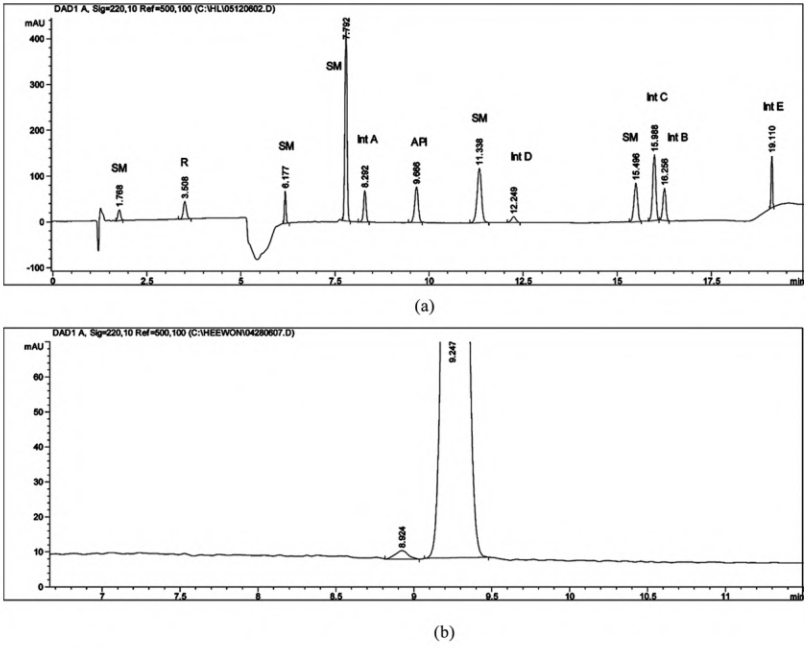


Figure 1. Case Study A: (a) Chromatographic separation of starting materials (SM), reagents (R), intermediates (Int), and API. (b) The HPLC chromatogram showing the impurity contained in the first batch of the drug substance.

HPLC chromatogram of the starting materials, reagents, intermediates, and the drug substance (i.e., API). This chromatogram was obtained from an artificial mixture of the involved compounds in order to illustrate the chromatographic separation. The intermediates and API were indicated on the chromatogram. This HPLC method was successfully utilized during the synthetic steps. The synthetic route involved a linear synthesis (intermediates A → B → C → D → E) for the production of API. This method was employed to profile impurities in the first batch of the drug substance. The batch did not have any detectible amount of intermediates, but there was an impurity in the level of 0.6% eluting right before the product shown in Figure 1(b).

In order to identify this unknown impurity, LC/MS experiments were performed. The experimental conditions of the HPLC method were transferred to LC/MS, except for the mobile phase composition. The 0.5% perchloric acid in the mobile phase A of the original HPLC method was substituted with 0.1% formic acid for LC/MS experiments for modifier volatility. This substitution did not affect the selectivity of the impurity from the drug substance considerably.

Figure 2(a) shows the total ion chromatograms (TIC) of the drug substance and the crystallization mother liquor. The retention time of the drug substance was 7.8 minutes and that of the impurity was 7.5 minutes. The mass spectra show the molecular ion for the drug substance and the impurity in Figure 2(b). The molecular ion of the desired product was observed at m/z 396, and the impurity showed an ion at m/z 378 with a mass difference of 18 amu. For tandem mass spectrometric experiments the mother liquor obtained from crystallization was utilized in order to obtain stronger signal intensity of the impurity.

One of the most widely used tandem mass spectrometric techniques using a triple quadrupole MS is the daughter ion (also known as fragment ion) scan. In this scan mode, the first quadrupole is set to pass only the ion of interest, usually the molecular ion. The second quadrupole is used as a collision cell with a controlled amount of collision gas, typically argon. The selected ion from the first quadrupole undergoes collision induced dissociation (CID) in the second quadrupole. The fragment (daughter) ions generated in the second quadrupole are then mass-resolved in the third quadrupole, generating structure-specific fragmentation information.

The MS/MS experiments were performed to obtain daughter ion spectra of the drug substance molecular ion at m/z 396. The fragmentation spectra were acquired at different collision energies (10, 20, 30, 40, 50 and 60 V) in order to cover various fragmentation patterns. The two representative spectra at different collision energies are shown in Figure 3(a). As expected, the molecular ion was still present and a few fragment ions were observed at low collision energies; and at

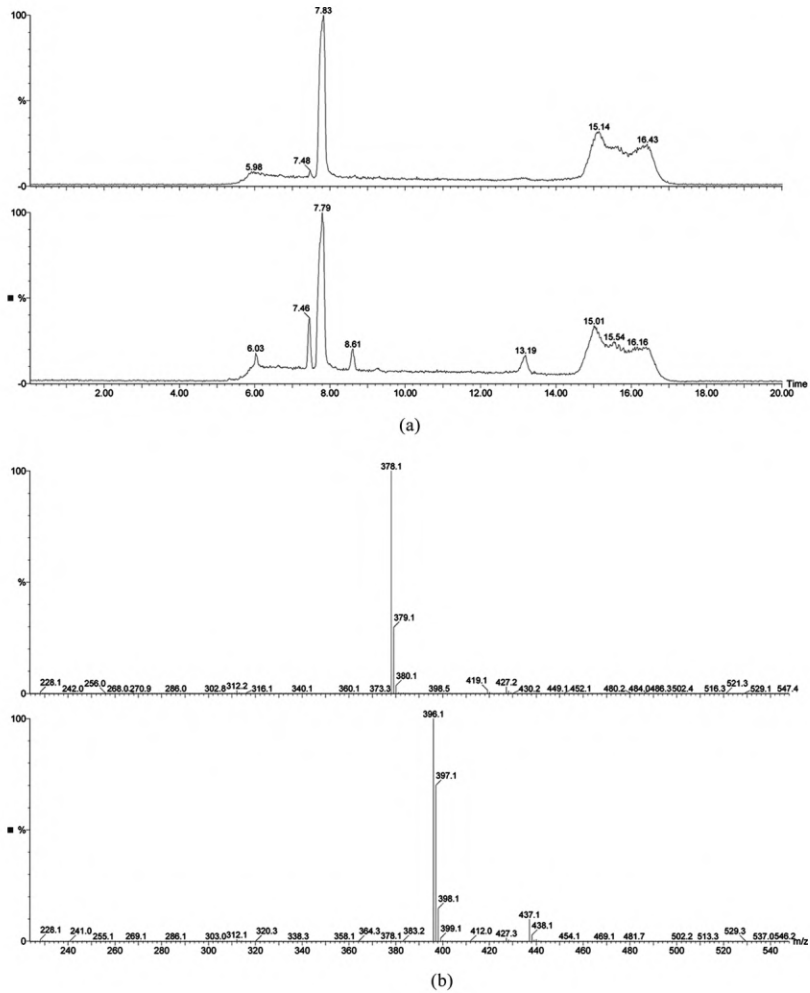


Figure 2. Case Study A: (a) Total ion chromatogram (TIC) of the drug substance (above) and the mother liquor (below). The retention time of the drug substance is 7.8 minutes and that of the impurity is 7.5 minutes. (b) The mass spectra show the molecular ion of the impurity at m/z 378 (above) and the drug substance at m/z 396 (below).

high collision energies the molecular ion disappeared and more extensive and smaller fragment ions were observed. The daughter ion scan of the impurity at m/z 378 showed a similar trend in Figure 3(b).

The illustrative structure of the drug substance is shown below with the key fragments observed in the daughter ion scan data. The mass

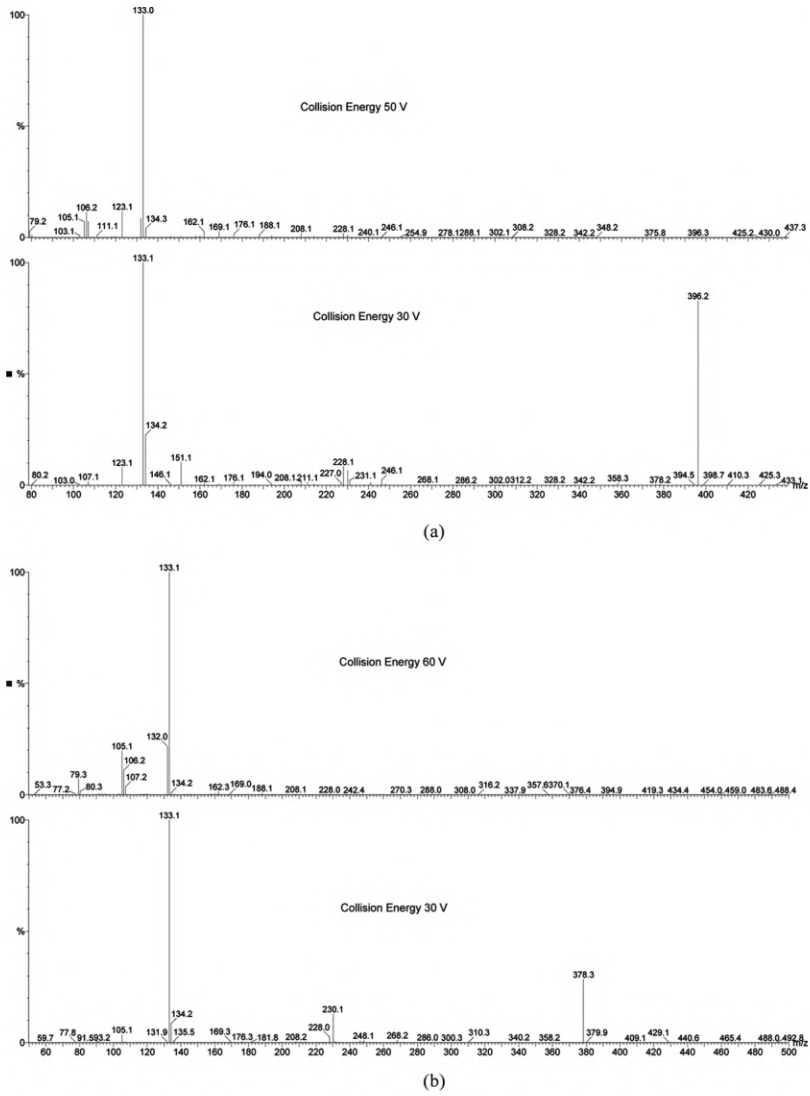
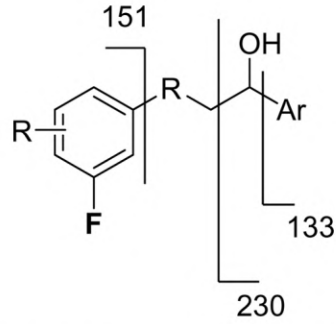


Figure 3. Case Study A: Fragment ion mass spectra at two difference collision energies are shown for the drug substance at m/z 396 (a) and for the impurity at m/z 378 (b).

difference of 18 between the drug substance and the impurity could be the loss of hydroxyl group ($-H_2O$) or the loss of the fluorine atom replaced with a hydrogen (-19 amu for fluorine $+1$ amu for hydrogen $= -18$ amu). Both the drug substance and the impurity had the fragment

ions at m/z 133 and m/z 230, indicating that the right hand side of the molecule was intact including hydroxyl functional group. However, the fragment ion at m/z 151 was present only in the drug substance daughter ion scan, noticeably absent in the daughter ion spectra of the impurity. Therefore, the difference between the drug substance and the impurity must have occurred in the left hand side of the molecule. Based on the data, the impurity was tentatively identified as the des-F (loss or removal of fluorine) of the drug substance. The ion corresponding to the m/z 151 of the des-F impurity would be m/z 133 (m/z 151–18) that happened to coincide with the m/z 133 from the right hand side of the molecule.



Structure of the drug substance with observed fragments for Case Study A.

The impurity was isolated using a Shimadzu preparative LC system in order to confirm the identity. The retention time of the impurity was 44 minutes and that of the drug substance was 47 minutes under the experimental conditions. The fractions collected were subject to high resolution mass spectrometry (HRMS) using an Agilent 1100 LC and an Agilent TOF (time-of-flight) mass spectrometer. The HRMS data showed the correct elemental formula for the drug substance with an error of 0.1212 ppm. The elemental formula based on the HRMS data of the impurity fraction matched that of the des-F impurity with an error of 2.3104 ppm.

The proposed des-F impurity was synthesized to confirm the identity unequivocally. The NMR data were acquired for both the impurity collected by preparative LC and the synthesized des-F API, and the NMR experiments confirmed that they were identical. In an effort to control the des-F impurity in the drug substance, corresponding des-F compounds for intermediates A, B, C, and D along the synthetic route were synthesized. The des-F intermediates A, C, and D were separated under the existing HPLC conditions as shown in Figure 4(a). The separation of intermediate B and des-F intermediate B was not ideal

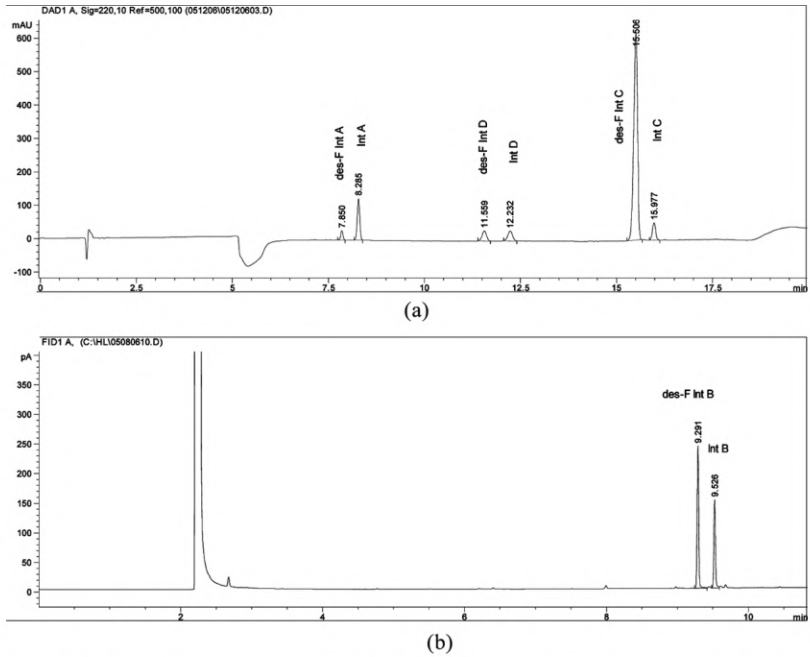


Figure 4. Case Study A: (a) HPLC chromatographic separation of the des-F intermediates A, C, and D from the corresponding intermediates for impurity control. (b) GC/FID method showing the separation of the des-F intermediate B from the intermediate B for impurity control.

in HPLC conditions, thus a GC/FID method was developed to follow the intermediate B as shown in Figure 4(b).

The HPLC/UV and GC/FID methods shown in Figure 4 were employed to carefully monitor the formation of des-F impurities along the synthetic pathway. It was found that the des-F impurity was formed from the chemical step of the intermediate A to the intermediate B, where an equimolar amount of lithium diisopropylamide (LDA) was employed. The formation of the des-F impurity was eliminated by slightly undercharging LDA.

In this case study, the structure of the unknown process impurity was proposed through LC/MS/MS and HRMS. The proposed structure was confirmed by preparative LC, synthesis of proposed compound, and NMR experiments. The origin of the impurity formation was pinpointed, and analytical methods were developed to follow and control the impurity formation throughout the synthesis. We were able to optimize the chemical synthesis so that the process did not generate the impurity.

Case Study B

The drug substance for this project was prepared as a free acid, and subsequently converted to a potassium salt. During the salt formation step a new impurity with an area percent of 2.4% was observed. The molecular ion $[M + H]^+$ for the drug substance was at m/z 642 (Figure 5), with one chlorine indicated by the isotope pattern. The molecular ion of the impurity was at m/z 638, four amu less than the API, clearly missing the isotope pattern of chlorine. As can be seen in the LC/MS data, molecular ions for both the drug substance and the impurity underwent significant in-source collision induced dissociation (CID) generating abundant fragmentation. The major fragment ions observed for the API were m/z 435, 338 and 267, with all three ions showing the pattern of one chlorine. The major fragment ions observed for the impurity were m/z 431, 334, and 263. Interestingly, all three ions were four amu less than the corresponding fragments in the API, and they lacked the chlorine isotope pattern.

In-source CID provided useful fragmentation data for these molecules without the need of a triple quadrupole mass spectrometer. The LC/MS/MS experiments were performed to obtain more detailed fragment ion spectra with a reduced noise level providing higher

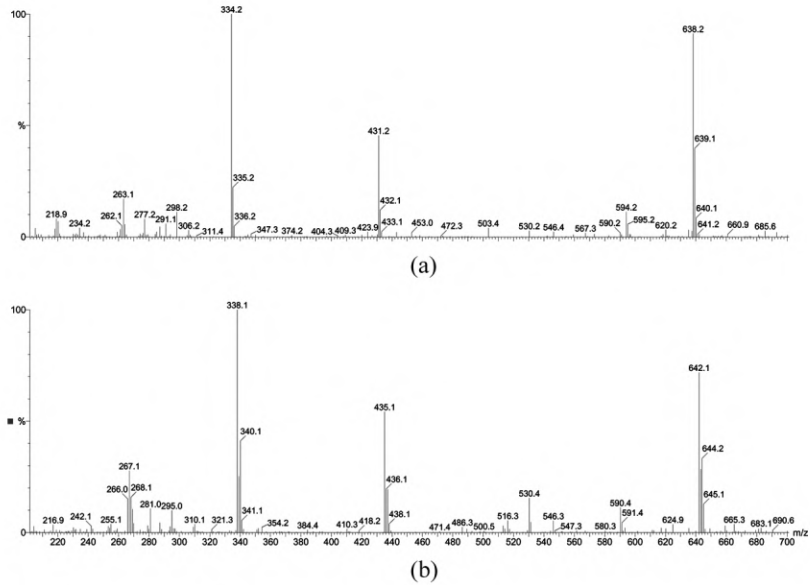
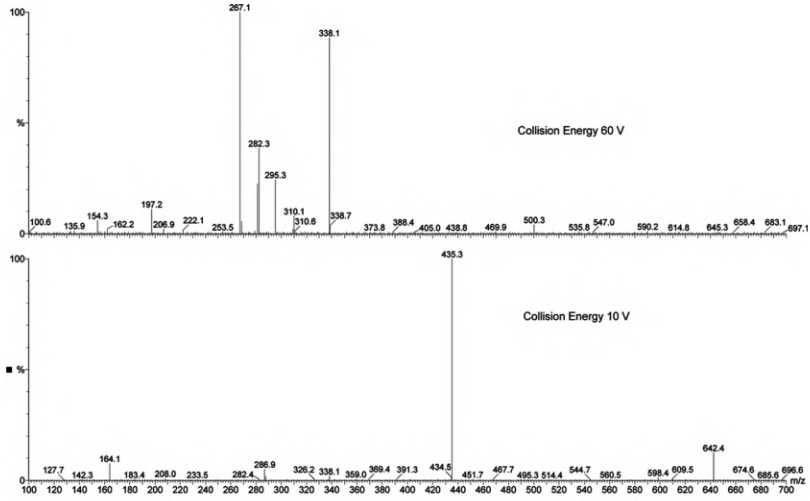
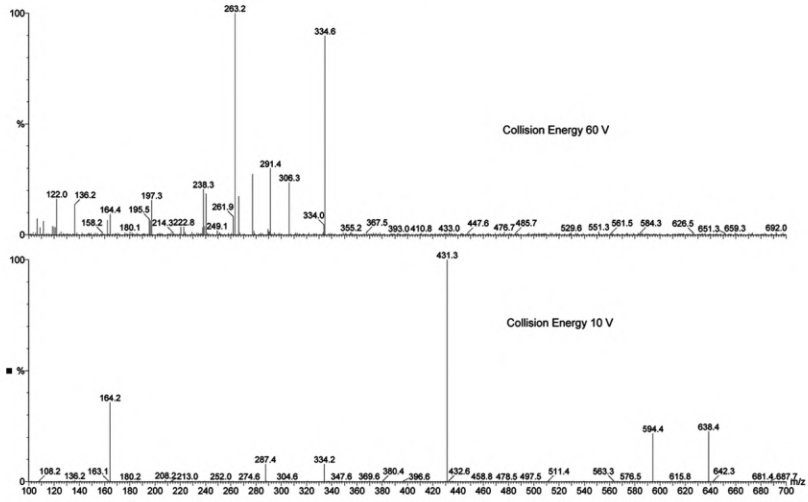


Figure 5. Case Study B: LC/MS spectra of the drug substance (below) and the impurity (above).

confidence. The daughter ion scan was carried out at different collision energies (10, 20, 30, 40, 50, and 60 V) in order to encompass a wide range of fragmentation. Two representative mass spectra at different collision energies are shown in Figure 6(a) for the API and in Figure 6(b) for the impurity. The major ions obtained with LC/MS experiments were still



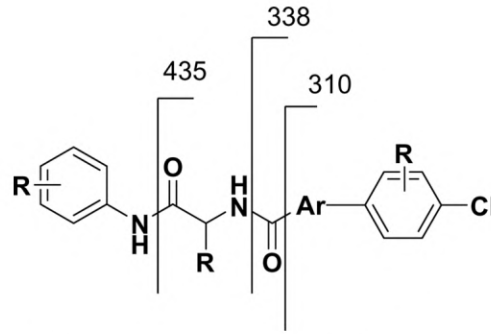
(a)



(b)

Figure 6. Case Study B: Fragment ion mass spectra at two different collision energies (a) for the drug substance at m/z 642 and (b) for the impurity at m/z 638.

the major fragments in the LC/MS/MS data including m/z 435, 338 and 267 for the API; m/z 431, 334, and 263 for the impurity. As the first quadrupole was set at the nominal mass resolution for the LC/MS/MS experiments, the chlorine isotope was filtered out, therefore, missing the isotope pattern information. The structure of the API with key fragments observed is shown below.



Structure of the drug substance with observed fragments for Case Study B.

There were two obvious pieces of information from the LC/MS and LC/MS/MS data. The first information was that the impurity was missing the chlorine, inferred from the molecular ion as well as the fragment ion isotope patterns. The second information was that all three major corresponding fragments of the impurity were four amu less than that of the API, indicating that the modification occurred on the right hand side of the molecule within the fragment structure of m/z 310. Since the molecule had to lose the chlorine, the most straightforward speculation was that "something" replaced the chlorine on the API. The nominal mass of the major isotope of chlorine is 35, therefore, in order to make the impurity to be 4 amu less than the API, "something" had to weigh 31 amu. The proposed impurity structure based on the information was that the chlorine was replaced with a methoxy ($-OCH_3$, 31 amu = 16 amu for O + 15 amu for CH_3) group. This made perfect sense as the salt formation was carried out with methanol as the solvent. The proposed impurity structure was further supported by HRMS experiments with an error of 2.5237 ppm. The salt formation step was successfully optimized with regard to the temperature, reagent addition rate, and reagent addition time in order to reduce the impurity formation.

Case Study C

Residual solvent analysis by GC is a routine analytical test performed for manufacturing of intermediates and drug substances. A GC/FID method including commonly used solvents was developed for this purpose and the conditions are described in the experimental section. One of the process intermediates was analyzed to quantify the residual amount of tetrahydrofuran (THF). The GC/FID data in Figure 7(a) showed a peak corresponding to THF at 6.9 minutes. There was a significant amount of an unexpected impurity present in the intermediate at a retention time of 13.4 minutes. GC/MS experiments were performed to acquire mass spectral data for the impurity. The ionization mode was positive electron impact (EI) ionization at 70 eV. Unlike electrospray ionization (ESI) which generally produces $[M + H]^+$ ions, electron impact (EI) ionization produces $M^{+\cdot}$ radical ions. Electron impact ionization is a "hard" ionization method producing significant

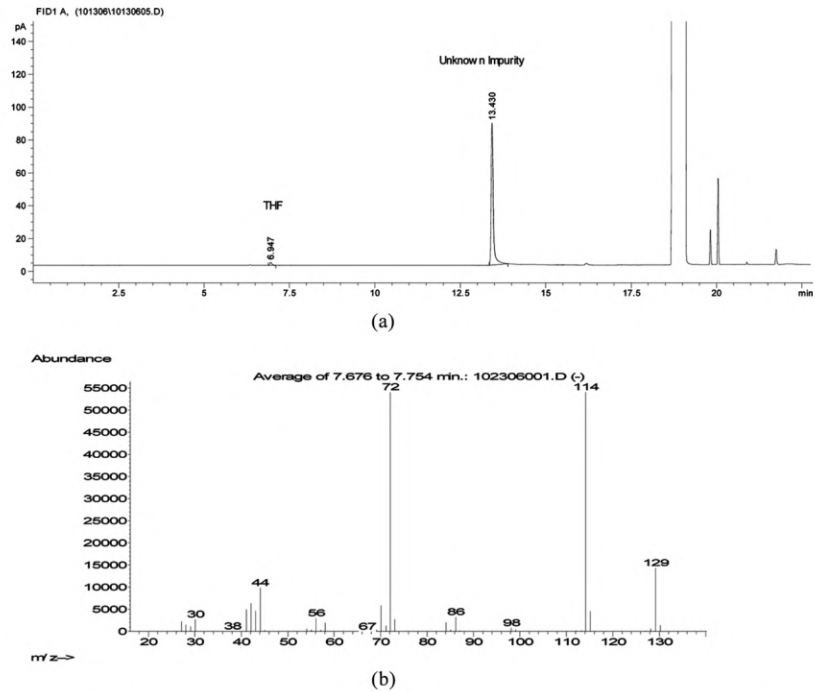
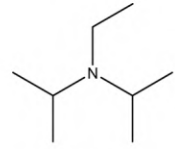


Figure 7. Case Study C: (a) GC/FID chromatogram showing the unknown impurity. (b) The EI-MS spectrum of the impurity obtained from GC/MS experiments.

fragmentation of the molecular ions, whereas electrospray ionization is known to be a "soft" ionization technique.[13,17,18] It is relatively easy to compare EI-MS sample data to the library data set and search, mainly due to the following two facts. First, the EI MS data are acquired and cataloged into commercially available libraries at the standardized 70 eV, thus the mass spectra are relatively consistent regardless of differences in manufacturers and instrumentations. Secondly, since it is a hard ionization technique EI-MS yields fragmentation spectra characteristic of the compound.

The mass spectrum acquired for the unknown impurity is shown in Figure 7(b). The library search of the mass spectrum returned diisopropyl ethyl amine (DIEA, also known as Hunig's base) with the highest score. The structure is shown below. The MS spectrum was generated by EI, therefore, the molecular ion observed was at m/z 129, the molecular weight of DIEA. The ion at m/z 114 showed a loss of a methyl group, and the ion at m/z 72 was the result of methyl and isopropyl group loss from the molecular ion. A sample of Hunig's base was analyzed as a standard and the retention time and mass spectral data confirmed the identity of the impurity. Subsequently, appropriate washes were implemented to remove Hunig's base for the preparation of this intermediate.



$C_8H_{19}N$
Exact Mass: 129.15
Mol. Wt.: 129.24

Structure of diisopropyl ethyl amine (DIEA).

CONCLUSION

Three case studies of impurity identification and control during the drug substance development were presented. It involved use of several analytical techniques complementing each other, including HPLC/UV, HPLC/MS, tandem mass spectrometry, preparative LC, HRMS, NMR, GC/FID and GC/MS.

Impurity identification of the case study A required a multidisciplinary approach, namely, generation of molecular ion and daughter ions using a range of MS/MS conditions, followed by preparative LC and reference synthesis by synthetic chemists, and

confirmation by HRMS and NMR. Subsequently, analytical methods were developed to follow the impurity throughout the synthetic pathway. In the case study B, the impurity proposed based on the tandem mass spectrometric data was immediately valuable and helped to improve process parameters. The availability of EI MS library for GC/MS made the impurity identification straightforward in the case study C.

It was demonstrated that by identifying the structure of the impurity, the origin of the impurity was pinpointed making elimination/reduction of the impurity achievable. Understanding of the impurity formation expands the knowledge of the process chemistry and enables control of the impurities.

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Exhibit 44

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July 6, 2021

Adam M. Slater
Mazie Slater Katz & Freeman
103 Eisenhower Parkway
Roseland, New Jersey 07068

Dear Mr. Slater:

At your request I have reviewed scientific literature, corporate documents, deposition testimony, and regulatory documents and standards, as set forth in this report and the attached Exhibits, and applied my education, training, and knowledge to provide opinions related to the contamination of valsartan manufactured by API manufacturers including ZHP, Hetero, Mylan, and Aurobindo with nitrosamines, and in particular NDMA and NDEA (the "contaminated valsartan"), and then incorporated into finished dose form by the same manufacturers, as well as finished dose manufacturers Teva and Torrent, who purchased the API from the API manufacturers (Teva from ZHP and Mylan, Torrent from ZHP) and incorporated the contaminated valsartan into their finished doses.

As set forth in detail herein, it is my opinion that the NDMA and NDEA levels found in the contaminated valsartan were completely avoidable and therefore are and were unreasonably dangerous, causing an increased risk for the development of cancer for those people ingesting the contaminated valsartan. All opinions set forth herein are held to a reasonable degree of scientific certainty, and have been formed based upon application of scientifically validated methodologies that I utilize in my own scientific work. My background and credentials are set forth in my curriculum vitae, which is attached hereto as Exhibit 1. The list of documents reviewed as part of my analysis is attached hereto as Exhibit 2. The list of scientific literature references specifically relied on for my opinions is attached hereto as Exhibit 3, with the caveat that the scientific literature relevant to the issues addressed is vast, and my familiarity with that literature certainly informs my knowledge in this field, as does all of my experience, even if not specifically listed.

Stephen S. Hecht

Stephen S. Hecht, Ph.D.
Wallin Professor of Cancer Prevention
American Cancer Society Professor
American Chemical Society Fellow

NCI Designated Comprehensive Cancer Center

I. Professional Background

I will first provide an overview of my professional background. I received my B.S. degree in chemistry (with honors) from Duke University in 1964 and my Ph.D. in organic chemistry from the Massachusetts Institute of Technology (MIT) in 1968. From 1968-69, I held a postdoctoral fellowship position at MIT in the laboratory of Professor Klaus Biemann, a pioneer in the application of mass spectrometry to organic chemical analysis. My research helped lay the groundwork for analysis of samples to be returned by NASA astronauts from the moon, and analyzed for trace organic molecules using mass spectrometry. I was an assistant professor of chemistry at Haverford College from 1969-1971, and a National Research Council Fellow at the U.S. Department of Agriculture from 1971-1973, carrying out research on practical applications for utilizing excess animal fat. My research career on nitrosamines began when I joined the American Health Foundation in 1973, initially as Head of the Section of Organic Chemistry in the Division of Environmental Carcinogenesis (1973-1980), then as Head of the Division of Chemical Carcinogenesis (1980-1996), and concurrently as Director of Research for the Foundation (1987-1996). The American Health Foundation was a private research institute founded by the eminent epidemiologist Ernst L. Wynder. I will discuss my research in more detail later, but I note here that I have carried out research related to nitrosamines continually since 1973. I have been continually funded for this research by the U.S. National Cancer Institute since 1975. Among a number of highly important contributions to the nitrosamine research field, my colleagues and I were the first to characterize "tobacco-specific nitrosamines" in tobacco products. These nitrosamines, among which are the powerful cancer causing agents NNK (Nicotine-derived nitrosamine ketone) and NNN (*N*-Nitrosonornicotine), considered "carcinogenic to humans" by the International Agency for Research on Cancer, are widely viewed as some of the main cancer causing agents in tobacco products. Our research paper in the 1978 Journal of the National Cancer Institute, describing these compounds, has been cited by the American Association for Cancer Research as a "Landmark in Cancer Research." In 1996, I relocated to the University of Minnesota where I hold my current position as Wallin Professor of Cancer Prevention, a "Land Grant Endowed Chair" in cancer prevention research. My academic appointment is in the Department of Laboratory Medicine and Pathology, in the University of Minnesota Medical School. I am also a member of the Medicinal Chemistry and Pharmacology graduate programs. From 1998-2014, I was the founding Head of the Carcinogenesis and Chemoprevention Program of the Masonic Cancer Center, University of Minnesota, a National Cancer Institute designated Comprehensive Cancer Center. I currently lead a research group of 10-15 scientists with B.S., M.S., or Ph.D. degrees in the chemical and biological sciences. Our research, which focuses on mechanisms and prevention of cancer induced by tobacco products and environmental agents, is fully funded by grants from the U.S. National Cancer Institute and the National Institute of Environmental Health Sciences. I am the principal investigator of three R01 grants and a program project (P01) grant, from the National Cancer Institute and co-investigator on a number of other grant and cooperative agreement awards from the National Institutes of Health and the Food

and Drug Administration. I have been awarded a Merit Award (10 years of funding) and an Outstanding Investigator Grant (14 years of funding) from the National Cancer Institute. My research has been recognized by a number of prestigious awards, including election as a Fellow of the American Association for the Advancement of Science, a Fellow of the American Chemical Society, and a Research Professor of the American Cancer Society. To the best of my knowledge, I am the only scientist who has ever held the latter two awards from the American Chemical Society and the American Cancer Society simultaneously. I received the American Association for Cancer Research/Cancer Research and Prevention Foundation Award for Excellence in Cancer Prevention Research in 2006 and the Founders Award from the Division of Chemical Toxicology, American Chemical Society, in 2009. I received the Joseph Cullen Award from the American Society of Preventive Oncology in 2012. I received the William Cahan Distinguished Professor Award from the Flight Attendant Medical Research Institute in 2002 and the Alton Ochsner Award Relating Smoking and Health in 2001. I received the Minnesota Award from the Minnesota Section of the American Chemical Society in 2017. I am a member of the Academy for Excellence in Health Research and the Academy for Excellence in Team Science at the University of Minnesota. My publication entitled "Tobacco Smoke Carcinogens and Lung Cancer", published in the Journal of the National Cancer Institute in 1999, can be found on the University of Minnesota Medical School "Wall of Scholarship" because it was cited more than 1,000 times in the peer-reviewed literature. I served as Editor-in-Chief of the American Chemical Society journal *Chemical Research in Toxicology* from 2013-2017 and as an Associate Editor of the *Journal of Medicinal Chemistry* from 2004-2012.

Respected researchers are invited by the National Institutes of Health as well as private foundations to serve on peer review groups for evaluation of research proposals submitted by scientists from the U.S. and abroad. I was chair of the "Chemo-Dietary Prevention Study Section" of the NIH from 2006-2009, and served on the "Chemical Pathology Study Section" from 1981-1985. I was on the Board of Scientific Counselors of the National Cancer Institute from 2001-2004. I served on the "Carcinogenesis, Nutrition, and the Environment Study Section" of the American Cancer Society from 1998-2001, and as its Chair in 2001. I served on the American Cancer Society "Council for Extramural Grants" from 2010-2014. I served on the "Grants Review Panel" for the American Institute for Cancer Research from 1984-1987. I currently serve, since 2011, on the National Cancer Institute "PREVENT Study Section." I continue to be in demand as an ad hoc member of multiple other peer review panels.

Numerous other service activities to the scientific research community are listed in my Curriculum Vitae. I note some of the more important ones here. I have served on multiple writing groups for the International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans. This important and prestigious series reviews and evaluates specific exposures and chemicals for evidence of carcinogenicity. Each committee member reviews a significant aspect of the literature and prepares a lengthy and detailed written

document. These documents are reviewed and discussed in a 10 day meeting in Lyon, France resulting in an evaluation of carcinogenic activity to humans and ultimately the publication of a monograph. The series is currently in Volume 127. I served on the Monograph Committees on "Tobacco Habits Other than Smoking," Volume 37, 1985; "Tobacco Smoke and Involuntary Smoking", Volume 83, 2002; "Betel Quid and Areca Nut," Volume 85, 2003, as committee Chair; "Smokeless Tobacco and Some Related Nitrosamines," Volume 89, 2004, and "A Review of Human Carcinogens; Lifestyle Factors," Volume 100E, 2009. I was a member of the National Toxicology Program Board of Scientific Counselors from 1997-2001 and the Science Advisory Board for the National Center for Toxicological Research from 1998-2002. I was on the Board of Scientific Counselors for the Division of Cancer Etiology of the National Cancer Institute from 1989-1995. I was Chair of the Division of Chemical Toxicology of the American Chemical Society from 1999-2000. I served on the Health Research Committee of the Health Effects Institute from 1992-1996. I have also served on numerous advisory groups for academic research centers specializing in toxicology and cancer research.

I am in demand as a speaker on topics pertinent to cancer prevention research, with particular emphasis on tobacco and cancer including basic, applied, and epidemiologic studies on nitrosamines. I have given formal invited lectures worldwide averaging about five per year since 2002 in almost every state of the U.S. and at scientific conferences and universities in Europe, Asia, and South America.

I have published over 880 original manuscripts, book chapters, reviews, and other peer reviewed documents in the scientific literature. This includes more than 600 original research articles in peer-reviewed journals. More than half of these original research articles are concerned with nitrosamines, including nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN). My H-index is 91, and my articles have been cited more than 35,000 times.

My first publication on nitrosamines was in 1974 when my colleagues and I discovered *N'*-nitrosonornicotine (NNN) in smokeless tobacco. This was the first example of a carcinogenic nitrosamine in unburned tobacco; in fact, the first example of any carcinogen in unburned tobacco. This paper was published in *Science*, and revolutionized the characterization and carcinogenicity assessment of tobacco products.

In the 1970s when my research on nitrosamines began, there was great interest in these compounds as potential carcinogenic constituents of food, drugs, tobacco products, and other consumer products. In 1956, Magee and Barnes had published their groundbreaking study demonstrating that NDMA caused liver cancer in rats. This was remarkable because NDMA is a water-soluble compound with only 11 atoms, and it had been supposed at the time, based on studies of polycyclic aromatic hydrocarbons, that carcinogenic agents were typically larger fat soluble compounds. The Magee and Barnes study stimulated an explosion of research on nitrosamines including extensive carcinogenicity testing and analysis

projects. Beginning in the 1970s, the U.S. Food and Drug Administration held regular meetings to address critical issues such as the contamination of bacon with *N*-nitrosopyrrolidine and related volatile nitrosamines including NDMA. Numerous analytical methods were developed for volatile nitrosamines such as NDMA in particular. The challenge was to be able to quantify relatively low levels of nitrosamine contaminants in common food and drug products. This was before the development and common use of highly sensitive mass spectrometers which are the current instruments of choice for the routine analysis of nitrosamines. Various methods were developed, but the one that was ultimately widely used was "Thermal Energy Analysis," in which the nitrosamine molecule was split and the released NO detected. This method was developed by a small company - Thermo Electron Corporation - now the huge instrument and scientific products corporation Thermo Fisher Scientific. The Thermal Energy Analyzer method was applied to numerous products and NDMA contamination was found in products such as beer, cured meats, and others. There was sufficient interest in nitrosamines in the period 1973-1996 that the International Agency for Research on Cancer sponsored biennial meetings for presentation of research on nitrosamines. These meetings were typically attended by 200-300 participants. Ultimately, the levels of common volatile nitrosamines such as DMN in most consumer products were decreased by process modifications and their concentrations rarely exceeded 5-10 ppb (0.005-0.01 ppm).

Our research on carcinogens in tobacco products fit very well into this framework of international interest, and we pursued it aggressively. Using my skills in analytical organic chemistry and mass spectrometry, and working together with an outstanding interdisciplinary team at the American Health Foundation, we carried out studies on the analysis of nitrosamines in tobacco products, the formation and synthesis of tobacco-specific nitrosamines, and the carcinogenicity of nitrosamines including tobacco-specific nitrosamines, cyclic nitrosamines, and other nitrosamines found in consumer products. We then extended our studies to investigate the metabolism of nitrosamines in laboratory animals and humans, and based on these studies developed biomarkers of nitrosamine exposure by quantifying nitrosamine metabolites in human urine. This research led to further investigations of human exposure to nitrosamines, particularly tobacco-specific nitrosamines. In a series of studies with significant policy implications, we demonstrated consistent exposure of non-smokers to carcinogenic tobacco-specific nitrosamines such as NNK via secondhand tobacco smoke in the home and a variety of commercial settings. These studies analyzed urinary NNAL, a metabolite of the lung carcinogen NNK, and contributed significantly to research supporting the clean air acts that have virtually eliminated indoor smoking, a known cause of lung cancer in non-smokers. Our studies on nitrosamine metabolism led logically to research on the interaction of their metabolites with DNA, the critical step in cancer induction by nitrosamines and other carcinogens. Our group characterized most of the DNA adducts formed by tobacco-specific nitrosamines and related cyclic nitrosamines. This research took advantage of my strong background in organic chemistry and analytical chemistry, particularly with the application of mass spectrometry.

Thus, as a result of more than 45 years of research in chemical and tobacco carcinogenesis, much of it focused on nitrosamines, I am thoroughly familiar with the state of the art in the formation, quantitative analysis, chemistry, biochemistry, metabolism, carcinogenicity, human exposure biomarkers, and DNA damage by nitrosamines. I currently serve on the European Food Safety Authority panel evaluating nitrosamines in food. I also served on the expert panel for the FDA Workshop entitled "Nitrosamines as Impurities in Drugs: Health Risk Assessment and Mitigation Public Workshop," March 29, 2021.

II. Nitrosamines

1. Chemical structures.

Nitrosamines are simple organic compounds formed by the attachment of an N=O group to an amino nitrogen.

2. Formation of nitrosamines

The formation of nitrosamines from secondary amines is textbook organic chemistry, a reaction familiar to all students in their first encounter with organic chemical reactions.[1,2] The nitrosation of secondary amines occurs so easily that it was once widely used in qualitative organic analysis as a test for the presence of a secondary amine, but after the discovery of nitrosamine carcinogenesis, this was eventually discontinued. Secondary amines such as dimethylamine and diethylamine are easily nitrosated by the agent nitrous anhydride (N_2O_3), which is formed from 2 molecules of nitrous acid (HNO_2), the conjugate acid of sodium nitrite ($NaNO_2$).[3] N_2O_3 reacts rapidly with a secondary amine such as dimethylamine or diethylamine to form the corresponding nitrosamine, in this case NDMA or *N*-nitrosodiethylamine (NDEA), respectively. The optimal pH for this sequence of reactions is 3.4, but it occurs over a wide range of pH values including at a pH 7 (neutral) with varying rates as expressed by the equation:

Rate = k [amine][nitrite]^2.

Tertiary amines can also be nitrosated to form dialkylnitrosamines such as NDMA.[4] Nitrosation of nicotine to produce NNK and NNN is a well-known example of tertiary amine nitrosation.[5] Nitrosation reactions can occur at neutral and basic pH with catalysis by formaldehyde[6] and can be inhibited by ascorbic acid.[7] Regarding the formation of NNK and NNN, we applied the known nitrosation chemistry to demonstrate that nicotine could be converted to 3 nitrosamines - NNK, NNN, and NNA.

This groundbreaking research established the chemical basis of nicotine nitrosation that eventually led to the identification of NNK in tobacco and tobacco smoke.[8,9] The identification of NNK in tobacco products then led to its testing for

carcinogenicity, which showed that it is a potent lung carcinogen in multiple animal species, independent of the route of administration, inducing mainly adenocarcinoma of the lung, now the major type of tumor seen in cigarette smokers.[10]

3. Analysis of nitrosamines

A great deal of effort has been devoted to the analysis of nitrosamines in various settings including food, drinking water, tobacco products, beer, medicines, and other consumer products. The rationale for these detailed and extensive studies derives from the powerful carcinogenicity of these compounds, for which the scientific community has consistently raised concerns about human exposure. Highly reliable analytical methods for determination of trace amounts of nitrosamines have existed for decades – first the nitrosamine specific "Thermal Energy Analysis" noted above and in more recent years sophisticated and sensitive mass spectrometric methods. All of these methods have been extensively validated for accuracy, precision, sensitivity, and overall reliability, and all existed prior to and during the development of the manufacturing processes at issue. The earlier analyses of preformed nitrosamines in food and beverages have been reviewed. In a representative summary, levels of "volatile nitrosamines" such as NDMA and NDEA in at least 60 different food types were recapitulated, typically being found in the 0-10 parts per billion range (micrograms per kilogram, or micrograms per liter), with occasional exceptions often involving foods preserved by smoking or related techniques. Levels of volatile nitrosamines in food are now generally lower in part because of regulations regarding the amount of nitrite that can be used.[11] A recent review has summarized current analytical data on human exposure to preformed nitrosamines.[12,] Nitrosamine levels in tobacco, food and beverages, drinking water, and personal care products were presented. The highest average levels were found in tobacco products (16,100 ng/g), followed by personal care products (1500 ng/g), while the lowest amounts were found in food and beverages (6.7 ng/g). Maximum average exposure to nitrosamines was estimated at about 25 µg per day, driven mainly by use of tobacco products.

4. Carcinogenicity of nitrosamines and NDMA in particular

In a landmark publication, Magee and Barnes first demonstrated the carcinogenicity of NDMA.[13] The substance was administered in the diet of rats (10 male and 10 female) at a concentration of 50 ppm. Between the 26th and 40th week, 19 of the treated animals developed primary hepatic tumors, with metastases in 7 cases. This remarkable finding initiated an entire branch of research ultimately resulting in the discovery of nitrosamines that readily and specifically induced tumors in virtually all major organs. High doses of NDMA are lethal; a median lethal dose in rodents of 20-40 mg/kg body weight has been reported.[14] The principal mechanism of death is severe hemorrhagic necrosis of the liver.[15] Consistent with this, cases of human poisoning by NDMA have been reported when large amounts of

the compound were used without precautions or when NDMA was used in deliberate attempted murders.[16]

The carcinogenicity of NDMA was demonstrated in several different strains of rats. Long-term administration of non-lethal doses of NDMA, typically about 4 mg/kg bw/day, consistently produced high incidences of hepatocellular carcinomas and cholangiocellular tumors. Short term administration of high doses of NDMA typically produced kidney tumors in multiple studies. The carcinogenicity of NDMA was significantly reduced by substitution of its methyl hydrogens with deuterium; the resulting deuterium isotope effect retarded its metabolic activation.[17] An extensive dose-response study of NDMA and NDEA on 4,080 rats demonstrated that a dose of 1 ppm of NDMA or NDEA in the drinking water caused about 25% of the rats to develop a liver neoplasm, a dose of 0.1 ppm caused about 2.5% to do so, and a dose of 0.01 ppm caused about 0.25% to do so, etc., with no indication of a "threshold."[18] In a study carried out by our group, the carcinogenic activities of NDMA and the tobacco-specific lung carcinogen NNK were compared.[19] Groups of 30 male F-344 rats were given 60 s.c. injections of 0.0055 mmol/kg of either NNK or NDMA over a 20 week period (total dose, 0.33 mmol/kg) and the experiment was terminated after 104 weeks. NDMA induced liver tumors in 6 of 30 rats; NNK induced a similar number of liver tumors but also a high incidence of lung adenocarcinoma and nasal cavity tumors.

The carcinogenicity of NDMA has been demonstrated in multiple species.[20] In Syrian golden hamsters, it induced various types of liver tumors when given by gavage or in the drinking water. Chinese hamsters and European hamsters also developed liver tumors when administered NDMA by injection. Guinea pigs developed liver tumors when given NDMA in the diet. Rabbits given NDMA in the diet developed liver carcinomas with lung metastases. Rainbow trout given NDMA in the diet developed hepatocellular tumors. Various strains of mice injected with NDMA developed liver and lung tumors. Liver tumors were also observed in mastomys administered NDMA by subcutaneous injection. Guppies and frogs exposed to NDMA in aquarium water resulted in the development of liver tumors. Rabbit, mink, blue fox, and duck are additional species in which NDMA induced liver tumors.

The pharmacokinetics and DNA binding of NDMA have been studied in detail in a range of species including mice, rats, rabbits, hamsters, dogs, pigs, and monkeys. Consistently, these studies have demonstrated high systemic clearance and high oral bioavailability of NDMA. In one study, NDMA was rapidly excreted into the saliva after i.v. and p.o. administration to dogs.[21] A consistent and linear pharmacokinetic and metabolic pattern emerged in these studies resulting in the conclusion that extrapolation to humans of conclusions obtained in studies using laboratory animals was justified.[22,23,24,25]

Similarly, the carcinogenicity of NDEA, which is more potent than NDMA, has been demonstrated in multiple species including in various different strains of rat,

mouse, and hamster as well as guinea pigs, chickens, rabbits, cats, dogs, pigs, monkeys, gerbils, snakes, hedgehogs, grass frogs, birds, and fish.[26] Dr. Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology, testified in his deposition that both NDMA and NDEA "are genotoxic carcinogens … in every experimental animal that they've been evaluated in" and are "demonstrated to produce tumors."[27]

In summary, NDMA and NDEA have been extensively tested in multiple species and at extremely low doses. Very few, if any, other chemicals have been so thoroughly tested for carcinogenicity, producing uniformly positive results. These data leave no doubt as to the high potency of NDMA and NDEA to induce tumors in laboratory animals and likely in humans. The lethality of NDMA at high doses has been observed in both laboratory animals and humans.

It is worth noting that both NDMA and a structurally related compound, dimethyl sulfate, are classified by IARC as belonging to Group 2A, "probably carcinogenic to humans."[28,29] According to the IARC Monographs preamble, this category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Of importance, IARC classification does not consider or indicate the strength of carcinogenicity. Thus, while NDMA is a far more potent carcinogen than dimethyl sulfate, both are classified as Group 2A. In an interesting exchange between Min Li of ZHP and ZHP's consulting toxicologist, Charles Wang, Ph.D., Dr. Wang advised that NDMA should actually be classified as Class 1B, stating: "Looks like IARC does consider NDMA as a Class 2A agent. However, according to the definition of Class 2 in ICH M7(R1) guideline, the Class 2 compound should be a 'Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)'. There are plenty rodent carcinogenicity data for NDMA (see revised report in the attached, page 4). In Fisher MSDS, NDMA has been classified as Class 1B for carcinogenicity (attached)."[30] In addition, NDMA is not classified in Group 1, "carcinogenic to humans", as there is no instance, other than the poisoning murder incidents noted above, in which humans have been exposed exclusively to relatively low doses of NDMA in the absence of other potentially carcinogenic exposures; exposure to nitrosamines always occurs in mixtures. The exception to this IARC classification is the tobacco-specific nitrosamines NNK and NNN, to which human exposure also occurs as mixtures with other tobacco constituents (their carcinogenic activities and concentrations in tobacco products, particularly smokeless tobacco, along with sufficient metabolic data, lead to the higher classification).[31] Carcinogenicity data for dimethyl sulfate were summarized in the IARC Monographs.[32] Of course, as recognized below, it would be unethical to perform studies on the effects of NDMA and NDEA on humans due to their potency, consistent with the routine use of nitrosamines to cause cancer in laboratory animals.

More than 200 nitrosamines of different chemical structures (e.g., different R groups attached to the N-N=O group) have been tested for carcinogenicity and at

least 199 of them cause tumors in laboratory animals.[33] Nitrosamines are frequently organospecific in these studies, meaning that, depending on the structure of the nitrosamine, specific organs or tissues may be affected. Thus, for NDMA, the main target tissues demonstrated in animal studies are the liver and kidney, independent of the route of administration and species in which the test is performed. NDEA also targets these tissues in addition to causing tumors of the esophagus. In contrast, di-*n*-butylnitrosamine causes mainly tumors of the urinary bladder in several different animal species, while methylbenzyl nitrosamine specifically causes esophageal tumors in rats. These organospecific characteristics of nitrosamine carcinogenesis have been linked to their metabolism in specific tissues. Metabolism is absolutely required for the carcinogenicity of nitrosamines and it has been established that α-hydroxylation (replacement of the hydrogen atom adjacent to the N-N=O group by a hydroxyl group) catalyzed by specific cytochrome P450 enzymes present in the liver and other tissues, is the major pathway of metabolism leading to carcinogenesis. Multiple human tissues contain these enzymes and can metabolize nitrosamines; therefore, it is likely that when exposed to nitrosamines, humans are susceptible to developing a wider spectrum of cancers targeting additional organs. There are some instances of concordance between target tissues of nitrosamine carcinogenesis in laboratory animals and in humans. One example is the tobacco-specific nitrosamine NNN, mentioned above. NNN causes esophageal and oral tumors in rats. A prospective epidemiology study carried out in male cigarette smokers in Shanghai demonstrated a strong relationship between NNN exposure (as determined by NNN in urine) and esophageal cancer in the study subjects. NNN is also the only strong oral carcinogen in smokeless tobacco, a known cause of oral cancer in humans.

5. Carcinogenicity of nitrosamines in humans

Exposure to nitrosamines, including NDMA and NDEA, is a likely cause of cancer in humans. For example, there are examples of human poisoning by NDMA which coincide with toxicity studies in rats, as noted above. Human metabolism of NDMA, NDEA, and other nitrosamines by the pathways known to lead to DNA damage - identical to that seen in rats that developed tumors upon treatment with these nitrosamines - has been demonstrated in numerous studies using various experimental systems. These included human liver slices, human liver subcellular fractions such as microsomes (with activity just as high as rat liver microsomes), and explant cultures of various human tissues including bronchus, esophagus, bladder, and colon.[34] These results are consistent with the known activities of human hepatic cytochrome P450 enzymes such as P450s 2E1 and 2A6, which efficiently metabolize NDMA and NDEA.[35] DNA adducts known to result from NDMA and NDEA such as 7-methylguanine and O^6-methylguanine have been detected in human tissues.[36,37,38]

Thus, pathways of metabolism and DNA damage observed in humans clearly replicate those in laboratory animals that developed tumors upon treatment with NDMA. There is no reason to doubt that humans are susceptible to carcinogenesis

by NDMA and NDEA, considering their powerful carcinogenicity and the immense amount of supporting biochemical and toxicological data which are available. For example, among all nitrosamines, the tobacco-specific nitrosamines NNN and NNK are widely recognized as human carcinogens because of the high levels of human exposure.[39,40,41] In a study of exposures to British workers in the rubber industry, it was concluded that, "Consistent with previous studies, *N*-nitrosamines exposures in the rubber industry, were associated with mortality from cancers of the bladder, lung, stomach, leukaemia, multiple myeloma, oesophasus, prostate, pancreas and liver."[42]

Collectively, these observations support the human carcinogenicity of nitrosamines in general, which are potent mutagenic carcinogens. There is no reason to expect that humans would differ from laboratory animals with respect to the existence of nitrosamine carcinogenesis. All of the main metabolic activation pathways of nitrosamines that occur in laboratory animals treated with these compounds also occur in human tissues. The DNA adducts that are formed are identical. For example, treatment of laboratory animals with NDMA causes the formation of 7-methylguanine and O^6-methylguanine in DNA; the latter is known to cause mutations, specifically G to A mutations.[43] The exact same DNA adducts and mutations are found in human tissues exposed to NDMA in vitro. Given sufficient exposure to NDMA and NDEA, as with the levels found in the contaminated valsartan (see below), the formation of these DNA adducts would be sufficient to cause mutations and cancer in exposed humans.

The World Health Organization published a peer reviewed analysis of the carcinogenicity of NDMA in 2002.[44] The findings include: "Based upon laboratory studies in which tumours have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic and clastogenic. …. Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure."[45] In the Effects Evaluation, with regard to Carcinogenicity, the study states: "The weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumour development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material. In available studies, NDMA has induced tumours in all species examined (mice, rats, hamsters), at relatively low doses in some cases, irrespective of the route of exposure (oral, inhalation); tumours were induced in a wide range of tissues, including the liver, Leydig cells, lungs, kidney, and nasal cavity, in the absence of significant non-neoplastic effects, in the limited number of studies in which these were well examined. …. NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed *in vitro*. …. DNA adducts (in particular, O6-methylguanine) formed by the methyldiazonium ion generated during metabolism likely play a critical role in NDMA carcinogenicity. …. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O6-methylguanine has been detected in human tissues exposed to NDMA. Therefore, owing to the

considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, and the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans."[46]

ZHP cited to the WHO article in its Deviation Investigation Reports, and Min Li, Ph.D., Vice-President for Analytical Operations for ZHP, confirmed that this was because the article was considered to be scientifically reliable.[47] Dr. Li, who holds a Ph.D. in Organic Chemistry from Johns Hopkins University, also confirmed that ZHP stated in its own Deviation Investigation Report that NDMA is, "a probable, you know, carcinogenic to human."[48] ZHP also stated in the Deviation Investigation Report for the TEA process that "NDEA is considered as a probably human carcinogen based on projection from the animal studies." ZHP cited to Pharmol. Ther., 1996, Vol. 71, Nos. 1/2, pp. 57-81 for this. ZHP also cited to Int. J. Biol. Sci. 2013, Vol. 9, No. 3, pp.237-245 for the observation that NDEA "is one of the most potent chemical hepatocarcinogens of this class, which can induce a variety of liver lesions in rodents."[49] Min Li also confirmed that there are no studies deliberately performed on humans with regard to the carcinogenicity of nitrosamines because it would be unethical to knowingly give NDMA to humans, as a result of the risk of cancer. More to the point, Min Li confirmed that it would be unethical "to give humans NDMA in the levels that were found in the valsartan pills."[50]

Min Li also testified with regard to information provided to ZHP by ZHP's consulting toxicologist, Charles Wang, Ph.D. Dr. Wang advised ZHP regarding the risk associated with the NDMA and NDEA in the valsartan, and his analysis was the basis for the toxicological assessment found in the Deviation Investigation Reports.[51] Min Li confirmed that Dr. Wang was consulted because he was deemed an expert who would be trusted to provide "reliable information."[52] Among other things, Dr. Wang advised ZHP that the classification of NDMA as a Class 2A agent was incorrect, and should instead be designated as Class 1B, since, "There are plenty rodent carcinogenicity data for NDMA."[53] In addition, Dr. Wang consulted what he termed, "a carcinogenicity expert consultant to perform the analysis who knows risk assessment of carcinogen and kept updated in regulatory guideline and standards in this field." In an email dated July 6, 2018, this expert, James McDonald, Ph.D., advised Dr. Wang – who relayed this information to Min Li - that, "the body of evidence on this suggests pretty clearly that this is a likely human carcinogen at sufficient exposures. The argument that the company would have to make to keep this product on the market will be very difficult with this profile. I'm not exactly sure where one would begin given the very high levels [his understanding was 30 ppm per a prior email from Dr. Wang] you think they are seeing. …. I expect this is not what they would want to hear but, unless there is a compelling reason to leave this product on the market (e.g.: only product available to treat a serious, life-threatening disease), I would expect the FDA would ask for a recall."[54]

Bandaru Venkata Ramarao, Vice President of Quality Control for Hetero Unit 5 (the finished dose manufacturing division of Hetero) also testified to the

significant carcinogenic risk presented by the NDMA contamination of Hetero's valsartan. In discussing the FMEA (Failure Modes and Effects Analysis) risk evaluation performed by Hetero, Mr. Ramarao testified that the severity of the hazard presented by the NDMA impurity, "was at the highest level because of the level of NDMA and because it's a probable carcinogen. . ." The Health Hazard was described in the FMEA as "Identified impurity is carcinogenic in nature," and he agreed this meant, "this is something that can cause cancer. . ." Finally, he confirmed that the overall risk priority number, or RPN, was the maximum possible score of 125, meaning it was deemed, "intolerable."[55] Mr. Ramarao was also asked about the 2002 WHO publication discussed above, and agreed that, "Because of these health effects that we are talking about and the risk of cancer, it would never be acceptable to knowingly sell valsartan containing NDMA... ....[T]hat's the reason why the valsartan that was sold by Unit 5 with the levels of NDMA that were seen, that never would have knowingly been done if you had known the NDMA was there because of that health risk."[56] Mr. Ramarao agreed that due to the GMP failures that resulted in the NDMA contamination, "the result of that was that NDMA ended up in the valsartan, which is something that causes cancer," and the risk, "was assessed at the highest level because people ingesting NDMA at the levels that were found in these pills is something that will increase their risk for cancer...."[57]

The likely carcinogenicity of NDMA (and NDEA) in humans is also demonstrated by regulatory guidelines. For example, the 2013 ICH M7 Draft Consensus Guideline, and 2015 ICH M7 Guidance for Industry, titled Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, include *N*-nitroso compounds in the "cohort of concern" of "high potency mutagenic carcinogens" that are excepted from the acceptable intake levels set forth for DNA reactive substances.[58] The same is found in the December 2008 FDA Draft Guidance for Industry titled Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches: "However, there are some compounds containing certain structural groups (aflatoxin-like-, *N*-nitroso-, and azoxy-structures) that have extremely high carcinogenic potency and are excluded from the threshold approach."[59] The EMA takes the same approach. In discussing a group of "high potency genotoxic carcinogens" including nitrosamines, the "Guidelines on the Limits of Genotoxic Impurities" in effect from January 2007 to January 2018, states in part: "Some structural groups were identified to be of such high potency that intakes even below the TTC would be associated with a high probability of a significant carcinogenic risk."[60]

Lance Molnar, Ph.D., Mylan's Senior Director, Global Pharmacology and Toxicology,, agreed in his deposition that nitrosamines are treated as non-threshold by "the EMA, FDA, ICH … regulatory bodies in general" and that "non-threshold effect would mean that a single molecule could be detrimental."[61] Accordingly, Mylan's Toxicology report stated that "[t]his potential for carcinogenic activity is considered the critical effect of these compounds (*N*-nitrosamines) as it can theoretically occur at doses far lower than those required to produce alternative

toxicities after either acute or repeated exposures."[62] Similarly, Mylan's Medical Risk Assessment stated the following: "the potential risk associated with potential exposure to NDEA above the defined specification is significant and [risk of harm to patients] cannot be excluded."[63]

Studies published in the dietary literature are of course quite significant to this analysis. One study concluded, "our results suggested that there was a positive association between NDMA intake and gastrointestinal cancer risk, specifically of rectal cancer."[64] Another study recognized "challenges to nutritional epidemiological research on the relationship between dietary nitrosamines and cancer occurrence," but found "an increased risk of colorectal cancer among individuals with a high intake of NDMA."[65] The authors of yet another study concluded in part, "According to our study, processed meat intake was positively associated with cancers of the oesophagus, stomach, colon, rectum, larynx, lung, breast, prostate, and urinary bladder. Therefore, processed meat could be said to act as a multi-organ carcinogen among humans." The authors pointed to nitrosamines as a potential causative agent.[66]

This body of literature also includes studies cited and analyzed in the 2002 WHO article discussed above, which includes Risch, H.A., Jain, M., Choi, N.W., Fodor, J.G., Pfeiffer, C.J., Howe, G.R., Harrison, L.W., Craib, K.J., and Miller, A.B. (1985) Dietary factors and the incidence of cancer of the stomach, *Am J Epidemiol. 122*, 947-59; González, C.A., Riboli, E., Badosa J., Batiste, E., Cardona, T., Pita, S., Sanz, J.M., Torrent, M., and Agudo A. (1994) *Nutritional factors and gastric cancer in Spain, Am J Epidemiol. 139*, 466-73; La Vecchia, C., D'Avanzo, B., Airoldi, L., Braga, C., and Decarli, A. (1995) Nitrosamine intake and gastric cancer risk, *Eur. J. Cancer Prev. 4*, 469-74; Pobel, D., Riboli, E., Cornée J., Hémon, B., and Guyader, M. (1995) Nitrosamine, nitrate and nitrite in relation to gastric cancer: a case-control study in Marseille, France, *Eur J Epidemiol. 11*, 67-73; Rogers, M.A., Vaughan, T.L., Davis, S., Thomas, D.B. (1995) Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer, *Cancer Epidemiol Biomarkers Prev. 4*, 29-36; Goodman, M.T., Hankin, J.H., Wilkens, L.R., and Kolonel, L.N. (1992) High-fat foods and the risk of lung cancer, *Epidemiology 3*, 288-99; De Stefani, E., Deneo-Pellegrini, H., Carzoglio, J.C., Ronco, A., Mendilaharsu, M. (1996) Dietary nitrosodimethylamine and the risk of lung cancer: a case-control study from Uruguay, *Cancer Epidemiol Biomarkers Prev. 5*, 679-82. In La Vecchia, et al., 1995, at 471, the authors concluded, "This study found a moderate but significant association between exogenous NDMA intake and gastric cancer risk. The association was consistently observed across strata of sex and age." In Gonzalez, et al., 1994, at 469, the authors commented on the association with gastric cancer, stating that they, "observed an increased risk associated with an elevated consumption of exogenous nitrosamines in both intestinal and diffuse types." In De Stefani, et al., 1996, at 681, the authors concluded, "In summary, NDMA intake was associated in this particular population with an increased risk of lung cancer." In Pobel, et al., 1995, at 70-71, the authors found: "In the present study we assess the risk of gastric cancer in relation to estimated dietary intake of nitrate, nitrite, and NDMA. The most important feature

revealed by this investigation is the increased risk associated with increasing intake of exogenous NDMA." In recognizing the complexity of the analysis, the authors concluded, "However, the findings presented here are consistent with the biological hypothesis and provide support for an association between nitrosamines and gastric cancer." In Goodman, et al., 1992, at 296, the authors concluded in part, "*N*-Nitroso compounds have been shown to be mutagens and important carcinogens for a number of target organs, such as the liver, stomach, brain, and lung. In this analysis, we found a strong relation between consumption of nitrite in men, and dimethylnitrosamines in men and women, and the risk of lung cancer." In Rogers, et al., 1995, at 33, the authors concluded in part that, "consumption of foods high in NDMA resulted in an elevated risk of cancer," in the "upper aero-digestive tract." In Risch et al., 1985, at 956, the authors concluded: "In summary, our data strongly suggest, in consonance with several previous studies, that nitrite intake is associated with risk of stomach cancer occurrence. Whether this relationship is mediated through the conversion of nitrite to *N*-nitroso compounds is unclear, although some protection appears to be afforded by consumption of citrus fruit."

To the extent these or other studies do not find a significant association, or raise questions, this can be explained by small or relatively small sample size, inadequate follow up period to capture all cancers, bias/inadequate dose quantification, potentially mitigating dietary factors such as vitamin C intake, and others.

Anticipating potential responses regarding proof of a cause and effect relationship, aside from the fact that a study cannot be ethically constructed to deliberately administer NDMA or NDEA to humans, this has been addressed. For example, in one article published in 1984 the authors noted the impediments to definitively proving cause and effect, "due to the insensitivity of the epidemiological instruments available today and to the lack of truly unexposed populations that could be used as controls." The authors stated in part, "Although a causal association between nitrosamine exposure and human cancer has not yet been rigorously established, the recognized association between exposure to nitrosamines in unburned tobacco products such as smokeless tobacco and oral cancer in humans is as close as one is likely to get in epidemiological studies of this class of carcinogens. In addition, biochemical, pathological, and experimental data provide little evidence that humans are resistant to the carcinogenic action of NOC [*N*-Nitroso compounds], from either preformed or endogenous sources… Although quantitative differences exist between rodents and humans in repair of DNA alkylation damage, the mechanisms of repair of this damage appear to be the same. Recently, malignant transformation of human pancreatic epithelial cells by NDMA has been reported."[67] A meta-analysis that noted varied results in studies that were reviewed, and the strengths and limitations of the study at hand, primarily based on difficulties in studying the effects of food intake, concluded in part that the risk of gastric cancer could be increased by "high consumption" of NDMA. The authors specifically noted: "When daily NDMA intake reached 0.12 ug, the harmful effect to human became more obvious."[68] For perspective, 0.12 ug (micrograms) is

equivalent to 120 ng (nanograms), and in a 320 mg dose of valsartan would equate to 0.375 ppm. These levels are in line with the levels established by the FDA, and were exceeded by the vast majority of the valsartan tested for nitrosamine contamination.

The EMA evaluated the valsartan contamination and concluded that the levels of NDMA and NDEA should be reduced to the maximum extent possible, but set thresholds consistent with the FDA's thresholds, factoring in the potential for nitrosamines to exist due to background levels for example in water. The statement firmly recognizes that there is no technically safe level, and the establishment of the thresholds is the product of a risk benefit analysis. Even though the EMA concluded that the risk is relatively low, that is also a finding of a real risk that is unacceptably dangerous, hence the establishment of the threshold levels.[69] Of interest as well, the EMA statement cites to and discusses a study performed in Denmark regarding the risk posed by the valsartan contamination, and found an increased risk for colorectal cancer and uterine cancer.[70] The EMA commented that the 4.6 year follow up interval was likely too short, and that the number of people studied too small, to draw any firm conclusions based on the data.[71]

A recently published study utilized data from a German health insurance database.[72] The cohort included those who filled at least one prescription of potentially contaminated valsartan from 2012 to 2017. The article refers to the establishment of whether or not the valsartan was manufactured utilizing API from ZHP, but without analysis of which manufacturing process was used. Thus, there is a concerning lack of data as to the extent to which those consuming potentially contaminated valsartan actually consumed contaminated valsartan. The endpoint was a cancer diagnosis. A statistically significant association for liver cancer was identified, but no association was identified for the overall risk of cancer or for other specific cancers. The authors pointed out that "molecular mechanisms known for NDMA in the pathogenesis of liver cancer in experimental animals support an association with NDMA exposure in humans. It may be that NDMA exposure promotes cancer development in already existing, as yet undiagnosed early stages and thus hastens clinical manifestation." They also recognized that, "The immediate recall of all potentially NDMA-contaminated valsartan drug products by regulatory authorities world wide was necessary in order to protect the public health." Thus, even with the limitations set forth in the study and discussed below, the study supports the conclusion that the contaminated valsartan increases the risk of cancer.

The study actually contrasts itself with Pottegard, discussed above in the context of the EMA statement, and points out the small number of people (5,150) evaluated in that study, and the small number of cancers in that study, and thus an inadequate sample size, by contrast to the large number of people studied in this study (780,871), which is a strength of the study. However, the study does recognize some significant limitations, including lack of information regarding the

NDMA content of the valsartan taken by those studied, and the short three year follow up.

Min Li, Ph.D. of ZHP testified with regard to a recent study published by Yoon et al. from South Korea.[73] Dr. Li testified suggested that this study supported the notion that NDMA would not increase the risk of cancer in a human.[74] The study addresses multiple limitations on its face and also suffers from a significant flaw that led the authors to retract the article. Yoon relied on a 2016 study by Zeng which found that "NDMA excreted in urine after ranitidine intake was 95.6 ng/mL, which was a 430-fold increase than before ranitidine use."[75] Yoon relied on those figures, and further added that "[a]ctual systemic NDMA exposure is likely much higher than that eliminated in urine."

The Zeng study collected urine samples of ranitidine users and tested the urine for NDMA. However, Zeng utilized GC-IT-MS for its analysis of urine samples. That test utilizes heat, and has been shown to cause residual ranitidine in the urine to form NDMA. Zeng was retracted on May 4, 2021 at the request of the authors: "[r]ecent research (1) has identified the potential for an analytical artefact associated with the use of gas chromatography that could have contributed to the levels of N-nitrosodimethylamine (NDMA) measured in urine samples containing ranitidine in this study. Given this artefact, the authors have informed the journal that their NDMA measurements are not reliable."[76]

On September 13, 2019, the FDA recommended the use of liquid chromatography with high resolution mass spectrometer (LC-HRMS) to measure levels of NDMA in ranitidine drug products, because gas chromatography (GC) based methods had been observed to elevate NDMA levels in tested materials.[77] On October 2, 2019, the FDA released a statement indicating that testing by LC-HRMS has shown the presence of much lower levels of NDMA in ranitidine.[78,79] On November 1, 2019, the FDA issued "Statement on new testing results, including low levels of impurities in ranitidine drugs." The statement indicated, "we have found levels of NDMA in ranitidine that are similar to the levels you would expect to be exposed to if you ate common foods like grilled or smoked meats. We also conducted tests that simulate what happens to ranitidine after it has been exposed to acid in the stomach with a normal diet and results of these test indicate that NDMA is not formed through this process. Similarly, if ranitidine is exposed to a simulated small intestine environment, NDMA is not formed." The FDA also stated that "[a]lthough many of these levels of NDMA observed through FDA testing are much lower than the levels some third-party scientists first claimed, some levels still exceed what the FDA considers acceptable for these medicines [96 nanograms of NDMA]."[80] The FDA tested various doses of ranitidine from eleven companies, three of which did not exceed 96 nanograms of NDMA.[81] None exceeded 1 microgram.[82] Thus, the study population included an unknown number of people who took uncontaminated valsartan. The Yoon study does not provide a compelling case to conclude that NDMA does not increase a human's risk of cancer when ingested at the levels seen with the contaminated valsartan.

III. Formation of Nitrosamines in the Valsartan API

As noted above, the formation of nitrosamines from secondary amines in the presence of nitrite and acid is absolutely basic organic chemistry. Any chemist who has taken even a basic organic chemistry course should know this. The test for a secondary amine was reaction with nitrite: a yellow oil, the nitrosamine, would be observed. A primary amine would produce bubbling due to the release of nitrogen from an unstable primary nitrosamine which rearranges to an unstable diazonium compound; a tertiary amine would not react (later shown to be not completely correct). Decades of research and volumes of published material clearly demonstrate that nitrite can react *easily* with amines to produce carcinogenic nitrosamines. The International Agency for Research on Cancer held international symposia on this issue every 2 – 3 years from the 1970s through the 1990s. The proceedings of these symposia are all available on the IARC website and describe hundreds of experiments demonstrating the ease of formation of carcinogenic nitrosamines in various settings including in chemical and drug manufacturing. For example, "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields *N*-nitrosodimethylamine."[83] Furthermore, the formation of nitrosamines in food cured with nitrite such as hot dogs and lunch meats has been extensively studied and documented. The U.S. Food and Drug Administration held regular meetings and symposia on this topic resulting eventually in significant decreases in the amounts of nitrite added to foods as a preservative. Volumes of research on nitrosamine contamination of various foods and tobacco products have been published. As set forth above, the FDA, ICH, and the EMA have all recognized the potential for nitrosamine impurities to exist in pharmaceuticals and the attendant risks. A qualified organic chemist in industry would be aware of this literature.

1. Nitrosamines in the ZHP API

I discuss the ZHP contamination in detail here to illustrate the root cause and the easy avoidability of the contamination. Ultimately, the manufacturers ignored basic chemistry principles, whether the root cause was reactions in the manufacturing process and/or cross-contamination due to solvent recovery or inadequate cleaning of equipment. The introduction of NDMA and NDEA into ZHP's Valsartan API was easily foreseeable. The Change Request Form for the Process Change for Valsartan Process II prepared on May 19, 2011, with an effective date of June 15, 2011[84] described the chemical processes, which included the addition of the solvent DMF, which was well known to decompose/degrade forming dimethylamine. "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of some acidic or basic materials."[85] "DMF ... Decomposes slightly at its normal boiling point to give small amounts of dimethylamine."[86]

There are multiple references in the Change Request Form to the need for process and method validation, and a reference to the need for testing including, "The residue of ZnCl2, and residue of solvents used in the process need to be tested for quality review." (Section 3). Unfortunately, from an organic chemistry perspective, ZHP failed to adequately evaluate the chemical processes, and failed to account for the risk of nitrosamine contamination. As a result, their risk assessment was inaccurate, i.e. "After evaluation, this change has a lower risk in terms of quality and safety,"[87] and "Synthetic route, intermediates remain the same and no adverse change in qualitative and quantitative impurity profile."[88] From the perspective of organic chemistry, as discussed herein and as recognized in ZHP's own root cause investigation (See ZHP Deviation Investigation Reports, ZHP00007221, PRINSTON0073443, PRINSTON0075797, PRINSTON0076100), a scientifically reasonable assessment of the Process Change would have identified the risk of formation of nitrosamine impurities, would have presumably led to testing for nitrosamines, and would have confirmed the formation was occurring. In addition, from an organic chemistry perspective this Change met the definition of a "Critical Change – A change which has direct or potential impact on product identity, strength, quality, purity and regulation, or have impact on validated Procedure, method, qualification or equipment."[89] This was a critical change because the process change had the foreseeable capacity to create, and resulted in, dangerous NDMA contamination. This analysis applies as well to the change from the TIN process to the TEA process with sodium nitrite quenching, which resulted in the formation of NDEA and NDMA. In light of the known potential results of the chemical processes, identification of the clearly foreseeable NDMA and NDEA impurity contamination could have been easily accomplished.

ZHP was certainly aware of the presence and significance of impurities in Valsartan API from the early days of their development of the original manufacturing process for Valsartan. For example, ZHP's knowledge of the significance of potential impurities was documented in the peer reviewed medical literature in 2006.[90] The article begins with a statement of the fundamental principle at the core of this litigation, that "The quality and safety of pharmaceuticals can be significantly affected by the presence of impurities. Consequently, the testing and establishment of limits for impurities in active pharmaceutical ingredients have become important initiatives by government and the pharmaceutical industry." The article, which included a co-author identified as an employee of ZHP, discussed available technologies for the detection and identification of impurities in API, in this instance Valsartan API.

Once the presence of NDMA was discovered, it was not difficult to determine the root cause. A July 27, 2017 email within ZHP refers to the root cause, specifically the fact that NDMA was known to occur in valsartan as a result of the use of sodium nitrite in the sodium azide quenching process, and that there was a need for, "the optimization of the valsartan sodium azide quenching process."[91] Dr. Li also confirmed that this was known to be a "common problem in the production and synthesis of Sartan APIs."[92] ZHP similarly concluded in a June 2018 document

summarizing the purported first detection of, and establishment of the root cause of the NDMA contamination, "this impurity is most likely generated during the 'azide quenching' by nitrous acid of the API manufacturing process."[93] The use of nitrite to decompose the azide reactant in the Valsartan synthesis process was a significant error due to the risk of nitrosamine formation, which should have been recognized. The use of nitrite should have raised a gigantic ***RED FLAG*** that nitrosamines could be present in the API. The same applies to the TEA process with sodium nitrite quenching.

Analysis of the Valsartan batches manufactured by ZHP with the zinc chloride process showed the presence of an unknown peak eluting just after toluene in the GC-MS analysis. On June 6, 2018, ZHP customer Novartis, which had contracted for further analysis of this API, notified ZHP that the unknown peak had been identified as NDMA. ZHP noted its failure to account for nitrosamines: "By looking into our CEP documents, it shows that NDMA is **not part of the controls in the current approved specifications** of the drug substance," and "Due to the fact that NDMA is a recently found **unexpected impurity** with the nature of probable carcinogen, and in order to understand the root cause for the occurrence of this impurity, ZHP has initiated root cause investigation."[94] It is important to note that ZHP's repeated statements that the NDMA was not known until June 2018 are contradicted by the July 27, 2017 email discussed herein, which not only references the fact that there was NDMA in the valsartan, but also the root cause tied to the sodium nitrite quenching.

The documents from ZHP clearly demonstrate how the formation of NDMA could have been avoided. They identified three critical factors: 1) use of dimethyl formamide in the tetrazole formation step, and the dimethyl formamide may have contained trace amounts of dimethylamine or the dimethylamine was formed during the process; 2) quenching of azide using nitrous acid (formed from nitrite under acidic conditions); and 3) quenching takes place in the presence of the product. ZHP concluded that NDMA was formed only when all 3 factors were present, based on extensive analysis by ZHP. Factor 2 should have raised a ***RED FLAG*** for the potential formation of nitrosamines. The contamination of dimethyl formamide with dimethylamine or the formation of dimethylamine during the process was foreseeable, and should have been evaluated. Factor 3 was shown to be critical to the problem; when the extraction of the product was performed prior to the addition of nitrite to quench the azide, no NDMA was observed, whereas in their original process, all samples were contaminated with NDMA. The results of the three factor analysis are perfectly clear and demonstrate a massive disregard for potential nitrosamine formation. Extraction prior to quenching would have been a simple remedy for the problem and should have been pursued. In their analyses of the product, they would not have identified NDMA in the chromatograms unless they were specifically looking for it, because the peaks would be too small. *But that is not a legitimate scientific excuse: ZHP should have been actively looking for nitrosamines based on the discussion above.* They could have used nitrosamine-selective methods such as combined gas chromatography-mass spectrometry for

this analysis. Using this or related methods, the detection of NDMA would have been straightforward.[95]

Prior to the process change from the "Process II" process to the Zinc Chloride process, which replaced Triethylamine with Zinc Chloride for the Tetrazole Ring Formation, and also replaced the original reaction solvent Toluene, with DMF (Dimethylformamide) and MTBE (Methyl tert-butyl ether), NDEA was similarly formed when 3 factors were present: 1) trimethylamine used as a catalyst for tetrazole formation; 2) nitrite used for decomposition of excess sodium azide; and 3) both factors 1 and 2 are together with the crude product. Lower amounts of NDEA were also formed due to trace amounts of diethylamine present in the trimethylamine used as a catalyst in the tetrazole formation step, and/or by direct nitrosation of trimethylamine. All of this was foreseeable, and if considered and tested for, the NDEA contamination would have been detected.

In the FDA inspection of ZHP,[96] numerous deficiencies were found, including 1)inadequate change control system; 2)inadequate validation program; 3)insufficient investigation of critical deviations; 4) the quality unit does not always fulfill the responsibilities of the quality unit; 5)cleaning procedures do not have sufficient detail; 6) equipment is not always of appropriate design;7)preventive maintenance procedures are not always adequate; 8) lubricants, heating fluids and coolants are not always food grade lubricants and oils; 9) sampling plans are not always scientifically sound; 10) stability studies are not always adequate; and 11) production deviations are not always thoroughly investigated. These deficiencies indicate a general disregard for potential problems in the manufacturing process, including the formation of nitrosamines. The report notes that while there is a procedure for investigating "out of specification/out of trend" deviations in the analysis of the product, it apparently is inconsistently applied.

In the specific investigation here, a peak eluting after the solvent toluene was ultimately definitively identified by an outside laboratory, using combined gas chromatography-mass spectrometry (GC-MS), as NDMA. The initial investigations disclosed by ZHP did not detect this peak due to errors in the headspace analysis process by its contractor, Zhejiang Haotian Testing and Technology Service, in which the vial was improperly crimped leading to non-detection of NDMA and any other peak.[97] This is apart from ZHP's confirmed knowledge at least as of July 2017 that there was NDMA in the valsartan.[98] The 5290 batches manufactured between 2016-2018 were reported to have contained an average of 57-64 parts per million of NDMA.

ZHP NDMA AND NDEA LEVELS:

The NDMA contamination levels confirmed in ZHP's contaminated valsartan were reported to range from 3.4 to 120 ppm, with variation between the East Zone and West Zone of the manufacturing facility, likely based on variations in the

production processes.[99] Additional documents establish even higher contamination levels.

In a document titled: Response to DMF Information Request Letter, ZHP provided the FDA with NDMA test results on residual solvents from three validation batches, as well as the NDMA Test Results for Batches Manufactured Using the ZnCl2 Process, presented as a chart of the results of testing of 783 batches manufactured between 12-28-2011 and 5-23-2018, with NDMA levels as high as 188.1 ppm.[100] These levels could have been established, for example using GC-MS, throughout the time that ZHP manufactured the valsartan API. This is demonstrated by the ease with which Novartis was able to identify NDMA. The same applies to the triethylamine manufacturing process with sodium nitrite quenching. In the Response to DMF Information Request Letter, ZHP reported NDMA levels for 55 batches that had been tested as of September 1, 2018, as high as 73.9 ppm.[101]

A separate spreadsheet provided by Solco to the FDA also documented the test results for the ZHP valsartan API batches manufactured with the zinc chloride process which were used to manufacture ZHP's finished dose for sale to Solco to be distributed in the United States, as well as the levels established by ZHP for the finished dose. There are a small number of batches with results in the single digits, with the lowest at 3.4 ppm, and the majority of the remaining batches have levels up to 188.1 ppm.[102] For context, 3.4 ppm translates to 1088 ng in a 320 mg pill, and 188.1 ppm translates to 60,192 ng in a 320 mg pill.

The ZHP Deviation Investigation Report dated November 11, 2018, titled Investigation regarding unknown impurity (genotoxic impurity) of Valsartan API (TEA process), provides NDEA levels for the TEA process valsartan API.[103] Testing of six validation batches established NDEA results of 0.03, 5.33, 12.77, 13.60, 18.83, and 13.51 ppm.[104] A separate table in that Report provides ranges and averages for the testing of 85 batches manufactured with the TEA process, documenting a range of 0.03-42.14, and average of 13.46, presumably in ppm. That table also sets forth NDEA levels in 111 batches manufactured with the zinc chloride process, documenting a range of 0-4.23 and average of 0.18, presumably in ppm.[105] As stated, since these impurities resulted from the manufacturing processes, all batches should be assumed to have been similarly contaminated, including those not tested.

Since we know that all batches of valsartan API manufactured with the zinc chloride process were contaminated with NDMA, the NDEA contamination would be additive and therefore further increase the risk of cancer for each pill manufactured from those batches. The TEA Deviation Investigation Report indicates that the likely cause of the NDEA contamination in the valsartan API manufactured with the zinc chloride process was cross-contamination due to shared equipment and solvent recovery.[106]

The aforesaid contamination of ZHP's valsartan API with nitrosamines including NDMA and NDEA, which are potent mutagenic carcinogens, resulted in an

unacceptable increased risk of cancer for those taking the medication. Thereafter, when aberrant peaks demonstrated unaccounted for impurities, the nitrosamine contamination could have been easily discovered based on knowledge of the potential chemical reactions and application of GC-MS to identify potential NDMA/NDEA. This was identified by Novartis even without the full information available to ZHP.[107] These failures and the consequent contamination of the Valsartan API resulted in the dangerous and unreasonable risk of causing or increasing the risk of causing cancer for those who ingested the contaminated valsartan with the reported levels of NDMA and NDEA.

No level of NDMA or NDEA in a pharmaceutical drug is "safe," in the sense that every exposure increases the risk to some incremental extent that one will develop cancer. The FDA set limits once the valsartan contamination was disclosed, and the aforesaid levels exceed the 96 nanogram/0.3 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDMA, and the 26.5 nanogram/.083 parts per million daily limit (based on 320 mg tablets) applied by the FDA to NDEA.[108] Those who ingested the contaminated valsartan above those levels sustained the unreasonably dangerous and unacceptable risk that this would cause or substantially contribute to causing cancer as a result of the NDMA and NDEA contamination.

It is important to note that the FDA's short term decision to delay the recall of the contaminated valsartan for a very brief period of time was not an endorsement of the safety of the medication.[109] Instead, this was the result of concern over the availability of the medication due to the widespread contamination, and a balancing of the risk of cancer against the more immediate risk of heart attack, stroke, or other life threatening results of a person abruptly ceasing the use of their hypertension medication.

2. Nitrosamines in the Hetero API

Hetero utilized a zinc chloride/DMF/sodium nitrite quenching process that was materially the same as ZHP's zinc chloride process, and the root cause of the NDMA impurity contamination of Hetero's valsartan was the same.[110] The reason for this occurring was the same as with ZHP. Mr. Ramarao confirmed this when he agreed with the following: "the most important problem" was that Hetero Unit 1 (API manufacturer) and Unit 5 (finished dose manufacturer) "never even realized the possibility that NDMA could form, so it was never actually looked for. That's the fundamental problem, correct?"[111]

The NDMA levels found on testing of Hetero's valsartan API manufactured with the zinc chloride process were confirmed in deposition testimony to range from 0.83 ppm to 7.78 ppm. This data was based on the testing of six batches, and was confirmed to be "representative of the contamination levels across the API – the Valsartan API that was sold from Unit 1 to Unit 5 and then sold in the United States."[112] As stated, since these impurities resulted from the manufacturing

process, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

3. Nitrosamines in the Aurobindo API

Aurobindo manufactured valsartan API for sale in the United States using a process referred to as the Toluene route, according to deposition testimony from Sanjay Singh, Associate President of North American Technical Operations.[113] The nitrosamine contamination of Aurobindo's valsartan API resulted from cross-contamination caused by a solvent vendor, Lantech. [114] The root causes of this cross-contamination included (1) a contaminated plate in a vertical heat exchanger that was shared between Aurobindo and Mylan, among others,[115] and caused residue to build up and carry over from batch to batch, causing NDEA contamination in the tri-*n*-butyl tin chloride[116] (Aurobindo's Chief Quality Officer analogized this to a dirty microwave),[117] (2) shared tanks (between Aurobindo, Mylan, and others) that were used to store the tri-*n*-butyl tin chloride resulting in NDEA contamination,[118] and (3) Lantech supplied the fresh solvent ethyl acetate which contained TEA,[119] and during the manufacturing process the TEA reacted with nitrosyl chloride, a byproduct of Aurobindo's API manufacturing process, resulting in NDEA contamination.[120]

Both NDMA and NDEA were detected in the valsartan API utilized by Aurobindo. The reported levels of NDEA ranged from 0.028 ppm to 1.508 ppm.[121] The levels of NDMA ranged from below .1 ppm to .129 ppm, and were additive to the NDEA levels, where present.[122] Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

4. Nitrosamines in the Mylan API

Mylan was vertically integrated and supplied valsartan API to Mylan's finished dose manufacturing facilities, and also supplied valsartan API to its sole external United States finished dose customer, Teva.[123] Mylan's root cause investigation found that NDEA was created in the solvent recovery process for o-xylene, the recovery layer of which contained traces of diethylamine and triethylamine, when it was recovered with nitrous acid, and carried over to the final API.[124] Mylan acknowledged that it was warned by its supplier as early as 2014 to

"avoid … nitrosating agents" with TEA due to the "possibility of formation of nitrosamines with nitrites or other nitrosating agents."[125]

Mylan confirmed that NDEA was present in every single API batch.[126] Mylan's API testing confirmed NDEA contamination in every API batch released to the US market, with levels between 0.1 ppm to 1.57 ppm.[127] Dr. Walt Owens, current Head of Global Regulatory Affairs and former Head of Global Quality, testified that "the API and finished dosage form [nitrosamine testing] results were essentially the same, you would be able to test the API alone."[128] Mylan's testing also showed that the valsartan API contained sporadic levels of NDMA contamination, in addition to the NDEA, including BQL, BDL, and from 0.01 ppm to 0.09 ppm.[129]Assuming the same solvent related practices were utilized with both the tested and untested batches, all batches should be assumed to have been similarly contaminated, including those not tested.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan manufactured by ZHP.

5. Nitrosamines in the Finished Dose Formulations

The NDMA and NDEA levels would be expected to be the same or nearly so in the finished dose formulations incorporating the contaminated valsartan API. This was addressed and confirmed in the deposition of Hai Wang, the President of Solco, ZHP's wholly owned distributor in the United States. Hai Wang confirmed that this was determined by ZHP and that data was provided to the FDA.[130] Both ZHP and Hetero were vertically integrated thus the above discussion of the causes and levels of the nitrosamine contamination of the API addresses the NDMA and NDEA contamination in their finished dose formulations as well.

Finished dose manufacturers Teva and Torrent obtained valsartan API from API manufacturers and then incorporated it into their finished dose formulations.

6. Nitrosamines in the Teva Finished Dose Formulation.

Teva manufactured and sold finished dose valsartan utilizing ZHP manufactured valsartan API, and Mylan manufactured valsartan API, labeled either as Teva or Actavis.[131] The valsartan finished dose labeled as Actavis and sold in the United States initially was manufactured using ZHP TEA process with sodium nitrite quenching valsartan API, and then ZHP zinc chloride process valsartan API beginning in late-2014.[132] The valsartan finished dose labeled as Teva was manufactured using Mylan valsartan API.[133]

ZHP reported NDMA levels to Teva between 0.8 ppm and 240.1 ppm.[134] Teva also tested 83 batches of ZHP valsartan API with NDMA levels of 30.01 ppm to 221.63 ppm.[135] In addition, Teva tested six batches of its finished dose valsartan

manufactured with ZHP valsartan API with NDMA levels of 14.8 ppm to 31.3 ppm.[136] It was confirmed that all ZHP valsartan API sold to Teva contained NDMA in excess of 0.3 ppm.[137] Daniel Barreto, Teva's former Senior Vice President Global Quality Compliance, testified that the finished dose product would have the same levels of NDMA as tested in the API and Teva "extrapolate[d] the nitrosamine test results of the API to the valsartan finished dose." [138]

Teva also tested for NDEA. Teva initially tested eleven batches of Mylan valsartan API and ten of the eleven batches had NDEA levels above 0.08 ppm, from 0.09 ppm to 0.50 ppm.[139] Teva tested 26 additional batches of Mylan valsartan API and twenty-four of the twenty-six batches tested above .08 ppm for NDEA, with results ranging from 0.08 ppm to 0.42 ppm.[140] Since the contamination occurred at the level of the API suppliers, the untested batches would be expected to have the same or very similar contamination levels as the tested batches, as discussed above.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan sold by Teva.

7. Nitrosamines in the Torrent Finished Dose Formulation.

Torrent purchased valsartan API from ZHP that was manufactured using the TEA with sodium nitrite quenching process. This was the only manufacturing process for ZHP valsartan API that was documented as being sold in the United States by Torrent.[141]

On August, 3, 2018, ZHP notified Torrent of "trace" amounts of NDMA in the Valsartan API sold to Torrent, which was the API manufactured using the ZHP TEA process with sodium nitrite quenching (as discussed above).[142] On Sept 7, 2018, ZHP notified Torrent that what ZHP described as, "another contaminant, NDEA, has been detected in the finished dose batches of valsartan."[143]

The levels of NDMA found on testing of the valsartan API purchased by Torrent from ZHP and then incorporated in its finished dose formulation sold in the United States were reported to range from 0.37 parts per million to 125.15 parts per million.[144] The levels of NDEA were found to range from 0.23 ppm to 16.93 ppm, with several batches found to be BDL and BQL range (Below Detection Limit and Below Quantification Limit).[145] All batches had NDMA and the majority had both NDMA and NDEA, which would increase the cancer risk. Since the contamination occurred at the level of the API supplier, ZHP, the untested batches would be expected to have the same or very similar contamination levels as the tested batches, as discussed above.

These contamination levels caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan sold by Torrent.

IV. Conclusion

The contamination of the valsartan API, and consequent contamination of the valsartan finished dose, as described above, caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting the valsartan. As described above, a range of cancers have been associated with intake of NDMA (and NDEA by extension). In general, the increased risk would likely be commensurate with the contamination levels, dosages, and periods of use. Therefore, people who ingested the valsartan with higher contamination levels and larger doses, over longer periods of time, would likely have a more substantial increased risk as opposed to those who ingested valsartan with lower contamination levels and lower doses, and for shorter periods of use. However, even those lower levels, lower dosages, and shorter periods of use present an unreasonable danger and risk, a risk to which one would not knowingly or deliberately expose a person.[146]

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https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan.

[109] U.S. Food & Drug Administration, FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity (July 13, 2018), https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.

[110] B.V. Ramarao Dep. Tr. 4/30/21, 372:15-373:23, 392:22-393:16.

[111] *Ibid.*, 425:16-24.

[112] *Ibid.*, 390:17-392:16.

[113] Sanjay Singh Dep. Tr. 5/20/2021, 32:24-33:9, 83:17-24.

[114] *Ibid.*, 390:15-391:8.

[115] *Ibid.*, 2021, 305:3-12.

[116] *Ibid.*, 180:4-181:7.

[117] *Ibid.*, 181:11-23.

[118] *Ibid.*, 204:10-24.

[119] *Ibid.*, 379:5-24.

[120] *Ibid.*, 380:1-18.

[121] For levels, see Auro-MDL-2875-0093561 (contains AuroLife batches); Auro-MDL-2875-0104586; Sanjay Singh Dep. Tr. 5/21/2021, 594:14-631:20.

[122] Auro-MDL-2875-0093561 (contains AuroLife batches); Auro-MDL-2875-0104586; Sanjay Singh Dep. Tr. 5/21/2021, 594:14-631:20.

[123] Derek GloverDep. Tr. 4/16/2021, 721:7-9; MYLAN-MDL2875-00429120, at 15.

[124] Daniel Snider Dep Tr., 3/31/ 2021, 237:12-238:1, 260:16-262:14; Derek Glover, Dep Tr. 3/12/2021, 439:1-440:7.

[125] MYLAN-MDL2875-00257214 (Pl-Glover 8); (PL-Glover 9); Derek Glover Dep Tr. 3/09/2021, 100:6-101:3; Daniel Snider Dep. Tr. 3/31/2021, 128:14-17.

[126] Antony Gomas Dep Tr. 4/09/2021, 54:13-55:7; Daniel Snider Dep Tr. 3/31/2021, 196:6-22.

[127] (Pl-Gomas 5); Antony Gomas Dep Tr. 4/09/2021, 100:10-106:5 (confirming that Pl-Gomas 5 reflects the most comprehensive nitrosamine testing results for Mylan API and FD), 111:15-112:8 (plain valsartan), 112:19-113:15 (valsartan HCTZ), 114:4-12 (amlodipine valsartan); Daniel Snider Dep Tr. March 31, 2021, 196:6-22.

[128] Walt Owens Dep Tr. 4/21/2021, 79:15-81:2.

[129] (Pl-Gomas 5); Antony Gomas Dep Tr. 4/09/2021, 100:10-106:5 (see above); Snider Dep. 264:9-16 (stating that Mylan believed that dimethylamine present in the triethylamine yielded NDMA that carried over into the final API and FD).

[130] Hai Wang Dep. Tr. 3/10/21, 116:3-118:23, 144:15-147:1.

[131] Teva 230; Michelle Osmian Dep. Tr. 5/06/2021, 33:2-236:24; 239:7-240:2.

[132] TEVA-MDL2875-00001886 (Sept. 9, 2014 Actavis Ltr. to FDA re CBE notice for ZHP manufacturing process change relating to ANDA 091519); TEVA-MDL2875-00013107 (Jan. 9, 2015 Actavis Ltr. to FDA re CBE notice for ZHP manufacturing process change relating to ANDA 090642); Daniel Barreto Dep. Tr. 4/14/2021, 106:23-108:16.

[133] TEVA-MDL2875-00320639-673, at -639.

[134] TEVA-MDL2875-00546489.

[135] *Ibid.*

[136] *Ibid.*
[137] Claire Lyons Dep. Tr. 4/27/2021, 130:3-132:2.
[138] Daniel Barreto Dep. Tr. 4/14/2021, 201:23-202:9; 275:9-276:5; 367:9-368:2.
[139] TEVA-MDL2875-00048605, at 61 of 61.
[140] *Ibid.*, 58-59.
[141] TORRENT-MDL2875-00072650; Sushil Jaiswal Dep. Tr. 6/04/20211, 67:21-24, 68:1-7.
[142] TORRENT-MDL2875-00131255; Reddy Neravetla Dep. Tr. 5/26/2021, 102:2-21.
[143] TORRENT-MDL2875-00504834; Jocelyn Rivera Dep. Tr. 02/22/2021, 438:5-24; Dawn Chitty Dep. Tr. 5/13/2021, 349:13-24, 350:1-4.
[144] TORRENT-MDL2875-00366172; Sushil Jaiswal Dep. Tr. 6/04/2021, 64:5-22, 65:7-24, 71:7-23, 86:17-24, 87:1-19.
[145] TORRENT-MDL2875-00135398; Dawn Chitty Dep. Tr. 5/13/2021, 59:15-24, 61:14-18.
[146] As recognized above, the FDA allowed contaminated valsartan to remain available for a short time in order to ensure there would not a shortage of this blood pressure medication in the short term. This decision was not an indication that the ingestion of the contaminated valsartan was considered to be safe or desirable.

Exhibit 45

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October 31, 2022

Adam M. Slater
Mazie Slater Katz & Freeman
103 Eisenhower Parkway
Roseland, New Jersey 07068

Dear Mr. Slater:

This report is a supplement to my report dated July 6, 2021, providing further discussion of the failure by ZHP to conduct a reasonable risk assessment of chemical reactions and necessary testing with regard to the TEA with sodium nitrite quenching process, and Zinc Chloride process, resulting in the manufacture and sale of valsartan API and finished dose contaminated with NDMA and NDEA. All opinions are stated to a reasonable degree of scientific certainty.

In summary, ZHP (and its subsidiary Shanghai Syncores that developed the zinc chloride process in the laboratory) could have and should have identified the risk of formation of nitrosamines including NDMA and NDEA, and utilized that information to test for and identify, and then prevent the nitrosamine impurities in the valsartan API and finished dose sold by ZHP. This could have and should have been done during and after development of the processes, and throughout the time that ZHP manufactured and sold the contaminated valsartan with those processes.

As stated in my July 6, 2021 report, the processes were flawed from the outset because of the inclusion of chemical reactions that could foreseeably create nitrosamines in the API. Specifically, quenching the sodium azide with sodium nitrite (nitrous acid) in the presence of the product, which led to a reaction between foreseeably created secondary amines and the nitrous acid to create NDMA/NDEA. For example, the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, established that the reactions forming nitrosamines including NDMA and the use of mass spectrometry to identify nitrosamines were well known. In this connection, Min Li confirmed that the reaction described in the IARC monograph, "the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA," is what occurred in the zinc chloride process, and this chemical reaction was known since 1865. (Min Li 4/21/21 Dep. Tr. 458:13-465:11).

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In addition, ZHP has acknowledged the likely occurrence of cross-contamination of valsartan API manufactured with the zinc chloride and TEA with sodium nitrite quenching processes on shared production lines. "During the period when multiple processes co-existed in Workshop 2 and Workshop W02, equipment were cleaned as per corresponding cleaning procedure to control the residue of active substance from the previous batch when switch from one process to another. However, the residual NDMA and NDEA in the equipment after cleaning for process switch were not analyzed…Based on the analysis of the NDMA and NDEA data, the original equipment cleaning procedure applied might not be able to get rid of the NDMA and NDEA residue on the equipment completely." The Report also states that there was a risk of cross-contamination due to solvent recovery for the same reason: ZHP was not looking for NDMA or NDEA because they failed to perform a straightforward assessment of the chemistry. (ZHP Deviation Investigation Report dated November 5, 2018 (DC-18003, PRINSTON0075797, at 126-130). Min Li of ZHP confirmed: "the DEA [diethylamine] is a typical process impurity of TEA, so DEA would also, yeah, would react with the nitrous acid to perform NDEA." With regard to NDMA, "in some of the TEA raw material it may contain a trace amount of, you know, of dimethylamine, okay, so that's one root cause…for some of the, you know, product, they were manufactured, you know, using the share line, you know, with the zinc chloride valsartan." (Min Li 4/20/21 Dep. Tr. 77:8-80:16). Varied NDMA levels were found in the valsartan API produced in the East and West zones at Chuannan, per the TEA process DIR. ZHP identified factors that would impact the NDMA levels. This includes, "number 1, temperature when adding sodium nitrite; number 2, charging speed of hydrochloride acid; number 3, ph control at the end; and number 4, aqueous phased separation time during quenching." In this connection, ZHP recognized that there was "a lack of detailed description in the production processes." ZHP further stated, "Due to the inaccurate description of some of the parameters in the process, there might be likelihood of fluctuation between different workshops or different batches manufactured in the same workshop, which eventually led to the difference in the amount of residual impurities…the residual amounts of NDMA in valsartan API batches." (Peng Dong 4/2/21 Dep. Tr., 536:7-543:2). Assessment and understanding of the potential chemical reactions in each process would have required testing for NDMA and NDEA of each batch of drug product manufactured with both processes, whether due to the process or cross-contamination, and would have shown the presence of NDMA and NDEA in each batch, as applicable.

The readily available scientific knowledge and testing should have been applied to identify the NDMA and NDEA even after the processes were adopted. This should have been apparent to any organic chemist involved in the development or assessment of these processes. Once ZHP went forward with the processes after having failed to detect and prevent the nitrosamine contamination during the development of the processes, ZHP could have and should have identified the nitrosamine impurities before selling the API or finished dose with NDMA/NDEA impurities. The same scientific knowledge and principles I have discussed with regard to the development of the processes was equally available and could and should have been applied when the product was manufactured for sale. This would have been as easy as adding appropriate testing for NDMA and NDEA to the specifications, and

testing each batch of API and finished dose accordingly. The result would have been detection of the nitrosamines.

ZHP has stated that the detection of the nitrosamines was not possible since they had no knowledge of the potential or actual presence of the nitrosamines and did not possess the technological ability to identify these impurities. I disagree. The deposition testimony provides context for this issue. For example:

Jun Du testified with regard to the August 26, 2018 letter written by ZHP (and signed by him) to the FDA, stating in part that, "it is not the residual DMF that reacts with nitrous acid of the next step, but rather it is the trace amount of dimethylamine, an impurity/degradant of DMF that reacts with nitrous acid to form NDMA, which adds a further dimension over the current thinking, logic and strategy for the evaluation of potential genotoxic impurities. It is this extra dimension over the current industry practice that obscured us from foreseeing this impurity during the process change from triethylamine process to zinc chloride process." (Jun Du 5/28/21 Dep. Tr. 232:18-234:6).

In the November 28, 2018 FDA Warning Letter to ZHP, the FDA explicitly, and correctly disagreed with ZHP's position that this could not be known, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change….Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree. We remind you that common industry practice may not always be consistent with cGMP requirements and that you are responsible for the quality of drugs you produce." (ZHP01344159 (ZHP 213)). Dr. Li and Mr. Du agreed with the FDA that ZHP was "responsible for the quality of the drugs" produced by ZHP. (Min Li 4/21/21 Dep. Tr., 426:8-427:5, 430:11-434:10) (Jun Du 5/28/21 Dep. Tr. 247:17-250:22).

The FDA also stated in the Warning Letter, "You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients." (Jun Du 5/28/21 Dep. Tr. 237:18-243:20). As stated in my prior report, the knowledge, technology, and methods to identify the NDMA and NDEA were readily available and should have been applied to identify the contamination, and this could and should have been done during development of the processes, and then again once ZHP began to manufacture valsartan with those processes for sale.

In this context, a draft of ZHP's deviation investigation report titled "Investigation Regarding an Unknown Impurity (Genotoxic Impurity)" stated that, "Due to insufficient extent and depth of process research at the early stage, as well as insufficient study and understanding of potential genotoxic impurities, only side reaction product and degradation

products were studied, and was unaware of the further reaction between degradation products and raw material." (Min Li 4/22/21 Dep. Tr. 528:5-531:4). This accurately describes the inadequate scientific risk assessment performed by ZHP, since the chemical reactions and means to test for the foreseeable creation of nitrosamines were well known and available. Scientifically reasonable process research, study and understanding of potential genotoxic impurities, would have resulted in recognition of the risk of creating the nitrosamine impurities, and testing that would have demonstrated the presence of these impurities. I know this from my own personal experience utilizing mass spectrometry to identify nitrosamines including NDMA beginning long before development of these processes in 2011, and the scientific literature including what is identified here and in my prior report, as well as in questioning of ZHP witnesses.

The focus on nitrosamines as potential human carcinogens began after the first demonstration of the carcinogenicity of dimethylnitrosamine in 1956 as outlined in my previous reports. The first report of nitrosamine contamination of food was published in 1968, and the first definitive evidence for the presence of dimethylnitrosamine in meat products in 1972.[1] This stimulated the development of reliable analytical methods for nitrosamines, layered on the existing knowledge base. A review published in 1976 notes the initial development of methods for the analysis of trace amounts of nitrosamines: "there is now no doubt that these compounds do occur in trace amounts in various environmental situations."[2] It goes on: "Recently a better standardization of the methodology, using gas-liquid chromatography and mass spectrometry, has yielded more reliable identification of the nitrosamines."

Fine et al reported the development of a highly sensitive and reliable nitrosamine-selective detector (the Thermal Energy Analyser, or TEA) in 1975.[3] Coupling of TEA to gas chromatography (GC-TEA) became the standard method for analysis of ultra-trace levels of nitrosamines. Thousands of products including pharmaceuticals were reliably analyzed and shown to contain trace amounts of nitrosamines (reviewed in Forman, D. and Shuker, D. Nitrate, nitrite and nitroso compounds in human cancer, *Cancer Surveys* 8: 205-487 (1989)), leading to international concern, further analyses, and mitigation efforts. Ultimately with the development of improved gas chromatography-mass spectrometry (GC-MS) methods and the wide availability of this instrumentation by the early 1980s, GC-TEA gave way to GC-MS which was even more reliable because of its ability to directly determine structural information from fragmentation patterns, information that was not available by GC-TEA. A review published in 1989 summarizes hundreds of analyses of nitrosamines in food.[4]

Thus, there is no doubt that the necessary technology and highly reliable methods for the analysis of nitrosamines in various settings were available from the 1970s. More recent analyses have confirmed the earlier data.

The international concern about the presence of these carcinogens in various settings gave rise to the widely attended and recognized International Agency for Research on Cancer conferences on nitrosamines which were held at various locations in the world from 1976-

1991. These meetings produced a series of books describing the research discussed at the meetings.[5]

In summary, nitrosamine contamination of food, drugs, and other products, and the reliable analytical methods to detect nitrosamines, have been known since the 1970s. Routes of formation of nitrosamines under various conditions have been extensively described in numerous publications and textbooks. Chemists using processes which involve the presence of nitrite and secondary amines should absolutely be aware of this huge body of literature, and utilize the widely available technology and methods to identify the nitrosamines resulting from these processes.

ZHP's witnesses acknowledged in their depositions that the chemical reactions were known and that mass spectrometry was available to identify nitrosamines starting before these processes were even developed. Dr. Li ultimately agreed that "the technology and the methodology was clearly available to identify the NDMA," as long as you "know what to look for" based on a risk assessment – which he confirmed is an ongoing process for the lifecycle of the drug. (Min Li 4/20/21 Dep. Tr., 230:9-19, 233:10-18).

Eric Gu also confirmed in his deposition that the 1978 IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" stated in part: "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrite at an acidic pH yields NDMA." (Eric Gu 4/5/21 Dep. Tr., 65:3-65:24). Mr. Gu was shown a 2009 article published in the scientific journal Tetrahedron Letters, titled: DMF, Much More Than a Solvent. The article states that "DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of acidic or basic materials..." He agreed that DMF could decompose to yield dimethylamine, and this was known in the scientific community. (Eric Gu 4/5/21 Dep. Tr., 172:13-174:9, 183:12-21).

Min Li was shown scientific literature identifying the risk of formation of nitrosamines during his deposition. This includes a textbook first published in 1996 titled, Purification of Laboratory Chemicals, which stated that DMF could decompose at its boiling point to yield dimethylamine. (Min Li 4/21/21 Dep. Tr. 391:13-395:5). Another 2009 scientific article titled "N.N-Dimethylformamide: much more than a solvent," also stated that DMF could decompose to produce dimethylamine, and this article cited a textbook published in 1966. (Min Li 4/21/21 Dep. Tr. 411:19-413:22). In addition, an article published in 2010 by a group from Beijing University of Technology in the Journal of Physical Chemistry titled "Theoretical Investigation of N-Nitrosdimethylamine Formation from Nitrosation of Triethylamine," described the formation of NDMA from the reaction of dimethylamine and nitrous acid. This is what occurred here with the zinc chloride process. (Min Li 4/21/21 Dep. Tr. 414:2-416:12). Dr. Li also stated that this was the reaction that occurred in the zinc chloride process: "the zinc chloride process for the formation of NDMA, you know, was also under the acidic, you know, pH. So, yes, so from that perspective, yeah, they are consistent." He also confirmed that in 2011, "scientists would be aware of and have available to them" this information, as well as

the known availability and use of mass spectrometry to test for potential nitrosamines, as stated in the 1978 Monograph, "The principal techniques employed for the analysis of volatile N-nitrosamines [including NDMA] have been described in a recent publication…The relative merits of high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is particularly important." (Min Li 4/21/21 Dep. Tr. 458:13-465:11). The literature discussed with the ZHP witnesses provides useful examples and is representative of information that was well known in the scientific literature and scientific community prior to and after the 2011 development of these processes.

The identification of the NDMA and NDEA would have been straightforward to anyone who was familiar with the chemical reactions in the manufacturing process, utilizing mass spectrometry. The location of the NDMA peak found on the chromatograms for the zinc chloride process has been identified by ZHP. For example, Min Li testified that there was a "little peak after the toluene peak" and stated, "And then in the sample injection, this peak turns out, if I remember correctly, to be n-butyl acetate, okay? So that's the peak - - that's the peak, you know, eluting after the toluene peak. Okay. So NDMA would elute on the shoulder, or sometimes may even completely co-elute with this peak." (Min Li 4/20/21 Dep. Tr. 25:16-28:22.). In addition, Qiangming Li confirmed that "[w]hen we used GC-FID for the testing, regarding the peak that appeared after toluene, the response of NDMA was pretty low." (Qiangming Li 4/14/2021 Dep. Tr. 168:17-20). The point is that taking into account the potential creation of nitrosamines should have led to the use of the GC-MS technology to identify the NDMA and NDEA.

A series of customer complaints was received by ZHP with regard to the unknown, or aberrant peaks on the chromatography. This included:

1. Ranbaxy/SunPharma on September 30, 2014 (Qiangming Li 4/14/2021 Dep. Tr. 130:7-170:11; ZHP01748896 (ZHP 260)).

2. Shanghai Pharmtech on November 20, 2014 (*Id.* at 177:22-199:20; ZHP01748905 (ZHP 264)).

3. SunPharma on November 17, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 290:16-318:10; ZHP00405069 (ZHP 277); ZHP01313866 (ZHP 278)).

4. Vertex on December 21, 2016 (Qiangming Li 4/14/2021 Dep. Tr. 204:11-214:17; ZHP02630924 (ZHP 265); ZHP02630926 (ZHP 266).

5. Glenmark on December 29, 2016 (Qiangming Li 4/15/2021 Dep. Tr. 254:22-290:4; ZHP00496153 (ZHP 271); ZHP00496155 (ZHP 272); ZHP02118712 (ZHP 273)).

6. Aurobindo on August 23, 2017 (*Id.* at 343:21-372:9; ZHP02094739 (ZHP 281)).

7. Novartis on May 22, 2018 (*Id.* at 386:17-466:17; ZHP00405021 (ZHP 284)).

Testing with the available technology would have identified the NDMA and NDEA at every point during the period when these processes were used to manufacture the valsartan. Novartis did what ZHP should have done. Novartis investigated the unknown peaks to determine what was causing them, and identified the NDMA in ZHP API manufactured with the Zinc Chloride process. Of note, Novartis inquired of ZHP as to whether DMF was utilized in the zinc chloride process on June 7, 2018, as part of its investigation. (ZHP01390017). This was relevant information to be taken into account by anyone assessing the cause of the unknown peaks since dimethylamine was the degradation/decomposition product of DMF that then reacted with the nitrous acid to form NDMA. ZHP simply ignored or didn't understand this basic chemistry. ZHP failed to perform the same analysis despite knowing the details of the manufacturing process, and this illustrates the inadequacy of ZHP's risk assessment from the perspective of organic chemistry.

I have reviewed chromatograms for the zinc chloride process. The NDMA peak would not have been identifiable as NDMA on the gas chromatography alone, but as stated above if ZHP had been diligent and conducted a scientifically reasonable assessment, they would have recognized the need to test for NDMA, and they could have used the available technology to identify the NDMA peak. We have examples of the results that would have been obtained in the documentation of the testing performed after the disclosure of the NDMA in June, 2018. The September 1, 2018 ZHP Response to DMF Information Request Letter provides a series of chromatograms showing the methods used, and the identification of the NDMA peak. (ZHP00079913). There was nothing complex or difficult about what was done once they were looking for the NDMA (and ultimately NDEA). In another example, the July 20, 2018 Deviation Investigation Report titled: Investigation regarding a Suspected Genotoxic Impurity of Valsartan (ZHP00004363) contains images of the June 6, 2018 email and attachments from Kevin O'Mahony to Xavier and others at ZHP. The chromatograms show the NDMA peak, and the method used to identify the peak, (ZHP00004399-4402). This should have been identified from the outset and at every other point moving forward, including when Novartis and other customers submitted complaints and inquiries regarding unknown peaks, as listed above. In this context, the European authority documented that Novartis had shared its analytical method with ZHP in July, 2017, in rebutting ZHP's argument that it did not have that information until June 2018. (ZHP01862681 (ZHP 232)). Of note, and perhaps not a coincidence, the July 27, 2017 email written by Jinsheng Lin, Ph.D. confirming that there was NDMA in ZHP's valsartan API, caused by the quenching with sodium nitrite, was written during the same month.

The same analysis applies to the NDEA in the valsartan. For example, August, 2018 testing performed by ZHP shows the NDEA peak identified. (ZHP02733180).

When asked why Novartis discovered that an unknown peak was due to NDMA before ZHP, he acknowledged that ZHP was required to investigate the peak, but could not give an explanation, "it was not so easy to detect" and "it's quite a challenging work." (Eric Gu 4/5/21

Dep. Tr., 210:24-219:5, 236:24-237:8). As set forth above, identification was quite feasible and should have been accomplished from the start of development of these processes, through the entire time that the drug products were manufactured and sold. This could have been done at any point, and seeming to contradict ZHP's position that it did not know, the July 27, 2017 email accurately describes the presence of the NDMA and the root cause of quenching with sodium nitrite.

Mr. Gu was questioned about the aberrant/unknown peaks. He had no reasonable explanation for why, despite every batch demonstrating the "NDMA peak just after the Toluene peak on the chromatograms. . . nobody at ZHP realized that it needed to be tested and identified." Mr. Gu admitted that ZHP was aware of these peaks and "did whatever they can," however, "They are struggling, I guess, in the past." (Eric Gu 4/6/21 Dep. Tr., 333:21-335:19). Mr. Gu was not aware that ZHP customer Sun Pharmaceuticals complained of unknown peaks in November 2016, and was not aware that, according to the European Medicines Agency, ZHP did not directly compare the unknown peaks observed by Novartis to ZHP's own gas chromatography. Nor was he aware that Novartis had shared its GC-FID method for evaluating chromatogram peaks with ZHP in July 2017. (Eric Gu 4/5/21 Dep. Tr., 240:3-243:18).

To be clear, the pathway to identification of the NDMA and NDEA impurities continued to be straightforward after the valsartan containing NDMA and NDEA began to be marketed. ZHP could have and should have taken the steps described above from the time they began to sell the valsartan containing NDMA and NDEA until it was discovered by Novartis, with the aid of an outside laboratory in June 2018. The necessary information and technology was readily available the entire time.

In addition to the ease in detecting the NDMA and NDEA with available testing, if ZHP still determined to go forward with these processes, the simple step of extracting the product prior to the quenching could have been taken to prevent the NDMA (and NDEA in the TEA with sodium nitrite process) formed in the zinc chloride process during quenching of the sodium azide from contaminating the drug product. ZHP stated in one document that, "any formation of NDMA will not be carried over into the product," and, "This approach can be done without any change of manufacturing process." July 1, 2018 Investigation of the Source of this Impurity (NDMA) (ZHP01495188). ZHP also provided a detailed analysis at pages 29-35 of 236 of the November 5, 2018 Deviation Investigation Report (PRINSTON0075797), indicating: "After optimization, the ROS remains the same, the product in Valsartan Crude Step (Step 4) is separated before the addition of NaNO2 (and the subsequent addition of Hcl)…Therefore, the product in the organic phase has no chance to be contaminated by NDMA." This would not have changed the manufacturing process for the drug product or route of synthesis as recognized by ZHP, and would not have negatively impacted or introduced any risk to the identity, quality, purity, strength, or stability of the drug products, since the drug product would have been separated from and not been exposed to contamination by the genotoxic impurities created during the quenching step. The same could have been done with the TEA with sodium nitrite quenching process. In the alternative,

ZHP could simply have gone back to the original process that did not involve sodium nitrite quenching, as "no NDMA or NDEA will be formed in Tin process." (November 5, 2018 Deviation Investigation Report, at 68 of 236, PRINSTON0075870).

Eric Gu confirmed that ZHP modified the zinc chloride manufacturing process after the FDA became aware of the NDMA, and agreed that ZHP's, "solution was to quench the azide separate from the product so it wouldn't become contaminated with the NDMA," and, "GC-MS would be used to evaluate all peaks to make sure that they were not genotoxic impurities that needed to be controlled out of the product." (Eric Gu 4/6/21 Dep. Tr., 455:1-458:15). If the solvents presenting the risk of secondary amines and sodium nitrite quenching were to be used, this would have prevented contamination of the drug product, and this testing would have confirmed the lack of NDMA or NDEA; this was absolutely feasible and could and should have been done from development through the entire course of the manufacturing of the drug product if the same solvents and chemicals were to be used in the process.

The ZHP API and Finished Dose Nitrosamine Levels
Are Materially the Same and All Exceed the FDA Levels

Minli Zhang—ZHP's Director of Finished Dose Formulation Quality—testified that ZHP determined its APIs' nitrosamines carried over to the finished dose. (3/26/2021 Minli Zhang Dep. Tr. 509:15-17, 518:18-519:3). Ms. Zhang explained:

> In our investigation report, we compared the NDMA level in the API and the NDMA level in the finished dose products, and we found the results basically matched each other. Therefore, we decided not to test the NDMA level in the finished dose products anymore.
>
> We could simply calculate based on the NDMA level in the API, as well as the amount of API used, to come up with a probable level of NDMA in the finished dose products.

(*Id.* at 521:8-19). This is the chart from the deviation investigation report:

In order to qualify the impurity relationship between the dosage form and API, some batches of API and corresponding dosage form were choose at random to test this impurity by Quality Research Department (QR), the testing result is as below:

表 1：制剂成品及对应 API 批次检测结果列表

Table 1: testing result between dosage form batches and corresponding API

序号 SN	产品名称 Product Name	产品批号 Batch No.	产品规格 Strength (mg)	API 厂家批号 Vendor batch No. Of API	API 结果 Result for API	制剂结果 Result for dosage form
					NDMA 含量(ppm) Assay of NDMA (ppm)	
1.	缬沙坦片 USP Valsartan Tablets USP	341A18007	40	C5523-17-382	81.4	83.1
2.	缬沙坦片 USP Valsartan Tablets USP	342B17012	80	C5523-17-190	101.9	101.0
				C5523-17-191	101.7	
3.	缬沙坦片 USP Valsartan Tablets USP	343G17002	160	C5355-17-132	120.0	110.3
				C5355-17-133	104.5	
4.	缬沙坦片 USP Valsartan Tablets USP	344B17071	320	C5355-17-131	119.3	123.2
				C5355-17-132	120.0	
5.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	609B18003	80/25	D5191-16-133	3.4	2.9
6.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17003	320/25	D5191-16-027	27.7	31.3
7.	缬沙坦氢氯噻嗪片 USP Valsartan HCTZ Tablets USP	611B17007	320/25	D5191-15-149	7.9	6.4

从上表数据分析，制剂产品与 API 的检测结果的差值接近(0.5~9.7ppm)。

Based on analysis above, the testing difference value of API and dosage form is almost the same (0.5-9.7ppm)

(ZHP00683571, 683578). As a result, ZHP stopped testing FD and blended the API levels to get the FD ones. (*Id.* at 520:22-523:19, 525:12-22 (discussing ZHP 189)). Hai Wang—the President of Solco—confirmed that the API and FD contained the same levels of nitrosamines. (3/10/2021 Hai Wang Dep. Tr., 116:3-118:23, 144:15-147:1). Prinston explicitly informed the FDA that "[i]t is confirmed that NDMA has been present in Valsartan drug substance (API) batches and carried to the drug product Valsartan," relying on the same test results as shown in the above chart. (PRINSTON00249966, 249967; ZHP00099424, 99441-42). ZHP concluded this analysis applied to NDEA as well. (PRINSTON0075797, 75977 (stating: "According to the previous raw material investigation, i.e. presence of diethylamine impurities in triethylamine hydrochloride, combined with the formation mechanism of NDEA, it should be the nitrosation of diethylamine impurities (in triethylamine hydrochloride) by nitrite to produce NDEA impurities, which is carried over into crude products, and finally remain in valsartan finished products.")).

As set forth in my July 6, 2021 report, testing by Teva and Torrent of its finished dose products manufactured using the ZHP contaminated valsartan API also established that the

levels of NDMA and NDEA all exceeded the limits set by the FDA. (TEVA-MDL2875-00546489 (TEVA 155); TORRENT-MDL2875-00005092; TORRENT-MDL2875-00369262; TORRENT-MDL2875-00072916; TORRENT-MDL2875-00366172).

Conclusion

The unreasonably dangerous contamination of valsartan drug products with NDMA and NDEA was easily avoidable, based on prevailing scientific knowledge and technology that existed before, during, and after the development and then commercial use of the zinc chloride and TEA with sodium nitrite quenching processes. The available knowledge and technology should have been applied to add straightforward testing for NDMA and NDEA of each batch of API and finished dose manufactured using the API manufactured with these processes, which would have revealed the presence of the NDMA and NDEA. The contamination of the drug product could have been prevented by extracting the product before quenching the sodium azide.

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[1] Sakshaug, J., Sognen, E., Hansen, M. A. & Koppang, N. Dimethylnitrosamine; its hepatotoxic effect in sheep and its occurrence in toxic batches of herring meal. *Nature* **206**, 1261-1262, doi:10.1038/2061261b0 (1965); Ender, F. & Ceh, L. Occurrence of nitrosamines in foodstuffs for human and animal consumption. Food Cosmet. Toxicol. 6, 569-571, doi:10.1016/0015-6264(68)90292-7 (1968); Ender, F. Ceh, L. Occurrence of nitrosamines in foodstuffs for human and animal consumption. Food Cosmet. Toxicol 6: 569-71 (1968).

[2] Magee, P. N., Montesano, R. & Preussmann, R. in *Chemical Carcinogens. ACS monograph 173* (ed Charles E. Searle) 491-625 (American Chemical Society, 1976).

[3] Fine, D. H. & Rounbehler, D. P. Trace analysis of volatile *N*-nitroso compounds by combined gas chromatography and thermal energy analysis. *J. Chromatog* **109**, 271-279 (1975).

[4] Hotchkiss, J. H. Preformed *N*-nitroso compounds in foods and beverages. *Cancer Surv* **8**, 295-321 (1989).

[5] International Agency for Research on Cancer (IARC) Books on Nitrosamine Research (each book, about 500 pages). IARC is a branch of WHO. *Environmental N-Nitroso Compounds: Analysis and Formation*, Vol. 1. (E.A. Walker, P. Bogovski, and L. Griciute, eds.), IARC Scientific Publications, No. 14, Lyon, France: International Agency for Research on Cancer, **1976**; *Environmental Aspects of N-Nitroso Compounds*, Vol. 1. (E.A. Walker, M. Castegnaro, L. Griciute, and R.E. Lyle, eds.), IARC Scientific Publications, No. 19, Lyon, France: International Agency for Research on Cancer, **1978**; *N-Nitroso Compounds: Analysis, Formation and Occurrence*. (E.A.

Walker, M. Castegnaro, L. Griciute, and M. Borzsonyi, eds.), IARC Scientific Publications, No. 31, Lyon, France: International Agency for Research on Cancer, **1980**; *N-Nitroso Compounds: Occurrence and Biological Effects*. (H. Bartsch, I.K. O'Neill, M. Castegnaro, M. Okada, and W. Davis, eds.), IARC Scientific Publications, No. 41, Lyon, France: International Agency for Research on Cancer, **1982**; *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*. (I.K. O'Neill, R.C. Von Borstel, C.T. Miller, J. Long, and H. Bartsch, eds.) IARC Scientific Publications, No. 57, Lyon, France: International Agency for Research on Cancer, **1984**; *The Relevance of N-Nitroso Compounds to Human Cancer: Exposures and Mechanisms*, Vol. 84. (H. Bartsch, I.K. O'Neill, and R. Schulte-Hermann, eds.), Lyon, France: IARC, **1987**; *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco and Mycotoxins*. (I.K. O'Neill, J. Chen, and H. Bartsch, eds.), IARC Scientific Publication, No. 105, Lyon, France: IARC, **1991**.

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EXHIBIT A
Supplemental List of Materials Reviewed

ZHP Documents

1. PRINSTON00249966, August 27, 2018 Letter from Prinston to the FDA regarding ANDA 206083.
2. ZHP02326538 (ZHP 189).
3. ZHP00662283, Draft Investigation regarding an unknown impurity (Genotoxic Impurity) (ZHO 212).
4. ZHP01862672, Final GMP Inspection Report (ZHP 232).
5. ZHP01748896, Email Chain between ZHP and Ranbaxy (ZHP 260).
6. ZHP01748905, Email Chain between ZHP and Shanghai Pharmttech Co. Ltd. (ZHP 264).
7. ZHP02630924, Email Chain regarding Vertex (ZHP 265).
8. ZHP02630926, Chronology regarding Vertex (ZHP 266),
9. ZHP00496153, Email Chain regarding Glenmark (ZHP 271).
10. ZHP00496155, Chronology regarding Glenmark (ZHP 272).
11. ZHP02118712, Email Chain between ZHP and Glenmark (ZHP 273).
12. ZHP00405069, Email Chain between ZHP and Sun Pharmaceutical Industries Ltd. (ZHP 277).
13. ZHP01313866, Chromatograms from Sun Pharmaceutical Industries Ltd. (ZHP 278).
14. ZHP02094739, Email Chain between ZHP and Aurobindo (ZHP 281).
15. ZHP00405021, Email Chain between ZHP and Novartis (ZHP 284).
16. ZHP00099424, Meeting Information Package from Prinston regarding ANDA 204821.
17. ZHP01390017, Email Chain Between ZHP and Novartis.
18. ZHP01495187, Investigation of the Source of this Impurity (NDMA).
19. ZHP01344159, November 29, 2018 Warning Letter from the FDA to ZHP (ZHP 213).
20. ZHP01495186, July 1, 2018 Email Enclosing ZHP01495187, Investigation of the Source of this Impurity (NDMA).
21. ZHP02733180, Chromatogram and Results for NDEA in ZHP's valsartan
22. PRINSTON00002249, 1-2 Annex-3 NDMA for TEA Process by GC-MS
23. ZHP02365339, Valsartan Chromatograms
24. ZHP02364173, NDMA and NDEA test results for all batches of Valsartan in USDMF grade
25. ZHP00011368, Certificate of analysis for D5191-14-157M
26. ZHP00344175, Summary of Unspecified Peaks in Residual Solvents Method of Valsartan
27. ZHP00476862, Valsartan Impurities Profile Analysis Report (ZHP 220)

28. ZHP00021455, Study Report of Unknown Peak in Residual Solvent of Valsartan
29. ZHP01870977, Study Report of Unknown Peak in Residual Solvent of Valsartan
30. ZHP02214602-71, Novartis Documents
31. ZHP02633528-ZHP02633538
32. ZHP00405024-ZHP00405068
33. ZHP00380568-ZHP00380591
34. ZHP01748896-ZHP01748899-ZHP1748899 (ZHP 260)
35. ZHP00405069-ZHP00405070 (ZHP 277)
36. ZHP01320376-ZHP01320392 (ZHP 280)
37. ZHP00405021-ZHP00405023 (ZHP 284)
38. ZHP00359796-ZHP00359822 (ZHP 288)
39. ZHP02135008-ZHP02135025 (ZHP 289)
40. ZHP02173090-ZHP00371269 (ZHP 290)

Torrent Documents

1. TORRENT-MDL2875-00072916, Details of Finished good batches (USA market) manufactured at indrad with Huahai API having old ROS.
2. TORRENT-MDL2875-00366172, Valsartan: Impact assessment of NDMA.
3. TORRENT-MDL2875-00369262, Test Results
4. TORRENT-MDL2875-00005092, Details of Finished good batches manufactured at indrad with Huahai API having old ROS.

Deposition Testimony

1. Minli Zhang Deposition Transcript for March 22-26, 2021.
2. Eric Gu Deposition Transcript for April 5-6, 2021.
3. Qiangming Li Deposition Transcript for April 13-16, 2021.
4. Jun Du Deposition Transcript for May 27,-28, 2021.

Literature

1. Sakshaug, J., Sognen, E., Hansen, M. A. & Koppang, N. Dimethylnitrosamine; its hepatotoxic effect in sheep and its occurrence in toxic batches of herring meal. *Nature* **206**, 1261-1262, doi:10.1038/2061261b0 (1965).
2. Ender, F. & Ceh, L. Occurrence of nitrosamines in foodstuffs for human and animal consumption. Food Cosmet. Toxicol. 6, 569-571, doi:10.1016/0015-6264(68)90292-7 (1968);
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6. Hotchkiss, J. H. Preformed *N*-nitroso compounds in foods and beverages. *Cancer Surv* **8**, 295-321 (1989).
7. *Environmental N-Nitroso Compounds: Analysis and Formation*, Vol. 1. (E.A. Walker, P. Bogovski, and L. Griciute, eds.), IARC Scientific Publications, No. 14, Lyon, France: International Agency for Research on Cancer, **1976**.
8. *Environmental Aspects of N-Nitroso Compounds*, Vol. 1. (E.A. Walker, M. Castegnaro, L. Griciute, and R.E. Lyle, eds.), IARC Scientific Publications, No. 19, Lyon, France: International Agency for Research on Cancer, **1978**.
9. *N-Nitroso Compounds: Analysis, Formation and Occurrence*. (E.A. Walker, M. Castegnaro, L. Griciute, and M. Borzsonyi, eds.), IARC Scientific Publications, No. 31, Lyon, France: International Agency for Research on Cancer, **1980**.
10. *N-Nitroso Compounds: Occurrence and Biological Effects*. (H. Bartsch, I.K. O'Neill, M. Castegnaro, M. Okada, and W. Davis, eds.), IARC Scientific Publications, No. 41, Lyon, France: International Agency for Research on Cancer, **1982**.
11. *N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer*. (I.K. O'Neill, R.C. Von Borstel, C.T. Miller, J. Long, and H. Bartsch, eds.) IARC Scientific Publications, No. 57, Lyon, France: International Agency for Research on Cancer, **1984**.
12. *The Relevance of N-Nitroso Compounds to Human Cancer: Exposures and Mechanisms*, Vol. 84. (H. Bartsch, I.K. O'Neill, and R. Schulte-Hermann, eds.), Lyon, France: IARC, **1987**.
13. *Relevance to Human Cancer of N-Nitroso Compounds, Tobacco and Mycotoxins*. (I.K. O'Neill, J. Chen, and H. Bartsch, eds.), IARC Scientific Publication, No. 105, Lyon, France: IARC, **1991**.

Exhibit 49

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q8(R2)
Document History

First Codification	History	Date

Parent Guideline: Pharmaceutical Development

Q8	Approval of the Guideline by the Steering Committee under *Step 2* and release for public consultation.	18 November 2004
Q8	Approval of the Guideline by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	10 November 2005

Annex to the Parent Guideline: Pharmaceutical Development

Annex to Q8	Approval of the Annex by the Steering Committee under *Step 2* and release for public consultation.	1 November 2007
Annex to Q8	Approval of the Annex by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	13 November 2008

Addition of Annex to the Parent Guideline

Q8(R1)	The parent guideline “Pharmaceutical Development” was recoded Q8(R1) following the addition of the Annex to the parent guideline.	November 2008

Current *Step 4* version

Q8(R2)	Corrigendum to titles of “Figure 2a” and “Figure 2b” of “Example 2” on page 23.	August 2009

PHARMACEUTICAL DEVELOPMENT

ICH Harmonised Tripartite Guideline

TABLE OF CONTENTS

PART I:
PHARMACEUTICAL DEVELOPMENT

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

1.1 Objective of the Guideline

This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (for definition, see ICH Q9) to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle* of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

1.2 Scope

This guideline is intended to provide guidance on the contents of Section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the Common Technical Document (ICH guideline M4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities.

2. PHARMACEUTICAL DEVELOPMENT

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space*, specifications, and manufacturing controls.

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products;

* See Glossary for definition

i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes and their controls. This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of post-approval submissions;
- real-time quality control, leading to a reduction of end-product release testing.

To realise this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters. This understanding can be gained by application of, for example, formal experimental designs*, process analytical technology (PAT)*, and/or prior knowledge. Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

The design and conduct of pharmaceutical development studies should be consistent with their intended scientific purpose. It should be recognized that the level of

* See Glossary for definition

knowledge gained, and not the volume of data, provides the basis for science-based submissions and their regulatory evaluation.

2.1 Components of the Drug Product

2.1.1 Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be inter-related and might need to be considered in combination.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended (e.g., Decision Tree #3 and #4 (Part 2)). This approach applies equally for the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification (3.2.S.4.5).

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2.1.2 Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids). Compatibility of excipients with other excipients, where relevant (for example, combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification (3.2.P.5.6).

Information to support the safety of excipients, when appropriate, should be cross-referenced (3.2.P.4.6).

2.2 Drug Product

2.2.1 Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug

product, taking into consideration intended usage and route of administration. Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

Any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in this section of the application; this justification can often be based on the experience gained during development or manufacture.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) that links clinical formulations to the proposed commercial formulation described in 3.2.P.1 should be summarized and a cross-reference to the studies (with study numbers) should be provided. Where attempts have been made to establish an in vitro/in vivo correlation, the results of those studies, and a cross-reference to the studies (with study numbers), should be provided in this section. A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Any special design features of the drug product (e.g., tablet score line, overfill, anti-counterfeiting measure as it affects the drug product) should be identified and a rationale provided for their use.

2.2.2 Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on the 1) amount of overage, 2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and 3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

2.2.3 Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the safety, performance or manufacturability of the drug product should be identified and discussed. This includes the physiological implications of drug substance and formulation attributes. Studies could include, for example, the development of a test for respirable fraction of an inhaled product. Similarly, information supporting the selection of dissolution vs.

disintegration testing, or other means to assure drug release, and the development and suitability of the chosen test, could be provided in this section. See also ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree #4 (Part 3) and Decision Tree #7 (Part 1) or ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The discussion should cross-reference any relevant stability data in 3.2.P.8.3.

2.3 Manufacturing Process Development

The selection, the control, and any improvement of the manufacturing process described in 3.2.P.3.3 (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification* (where applicable), and any process control requirements. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification (3.2.P.5.6).

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the process described in 3.2.P.3.3 should be discussed. The discussion should summarise the influence of the differences on the performance, manufacturability and quality of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (3.2.P.5.4). The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

In order to provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end-points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described.

* See Glossary for definition

An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness* can be useful in risk assessment and risk reduction (see ICH *Q9 Quality Risk Management* glossary for definition) and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (see ICH *Q9 Quality Risk Management*).

2.4 Container Closure System

The choice and rationale for selection of the container closure system for the commercial product (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

The choice of primary packaging materials should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included, when relevant.

If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions which, as far as possible, simulate the use of the product.

2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the drug product should be discussed in this section (3.2.P.2.5). The discussion should include, for example:

- The rationale for performing or not performing microbial limits testing for non sterile drug products (e.g., Decision Tree #8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products)*;
- The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial;
- For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination.

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling micro-

* See Glossary for definition

organisms by using an antimicrobial preservative effectiveness test. The concentration used should be justified in terms of efficacy and safety, such that the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product is used. Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section.

2.6 Compatibility

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration (e.g., product added to large volume infusion containers) might need to be addressed.

3. GLOSSARY

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Formal Experimental Design:

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “Design of Experiments”.

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product’s discontinuation.

Process Analytical Technology (PAT):

A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Robustness:

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Quality:

The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity (from ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*).

PART II:
PHARMACEUTICAL DEVELOPMENT - ANNEX

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 13 November 2008, this guideline is recommended for adoption to the three regulatory parties to ICH

1. INTRODUCTION

This guideline is an annex to ICH Q8 Pharmaceutical Development and provides further clarification of key concepts outlined in the core guideline. In addition, this annex describes the principles of quality by design[1] (QbD). The annex is not intended to establish new standards or to introduce new regulatory requirements; however, it shows how concepts and tools (e.g., design space[1]) outlined in the parent Q8 document could be put into practice by the applicant for all dosage forms. Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, opportunities arise to enhance science- and risk-based regulatory approaches (see ICH Q10, Pharmaceutical Quality System).

Approaches to Pharmaceutical Development

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. An illustration of the potential contrasts of these approaches is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle[1] of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Pharmaceutical development should include, at a minimum, the following elements:

[1] See glossary

- Defining the quality target product profile[1] (QTPP) as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, strength, and stability;
- Identifying potential critical quality attributes[1] (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled;
- Determining the critical quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality[1];
- Selecting an appropriate manufacturing process ;
- Defining a control strategy[1].

An enhanced, quality by design approach to product development would additionally include the following elements:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including;
    - Identifying, through e.g., prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs;
    - Determining the functional relationships that link material attributes and process parameters to product CQAs;
- Using the enhanced product and process understanding in combination with quality risk management to establish an appropriate control strategy which can, for example, include a proposal for a design space(s) and/or real-time release testing[1].

As a result, this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (See ICH Q10).

2. ELEMENTS OF PHARMACEUTICAL DEVELOPMENT

The section that follows elaborates on possible approaches to gaining a more systematic, enhanced understanding of the product and process under development. The examples given are purely illustrative and are not intended to create new regulatory requirements.

2.1 Quality Target Product Profile

The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;

[1] See glossary

- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

2.2 Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.

CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs.

Potential drug product CQAs derived from the quality target product profile and/or prior knowledge are used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

2.3 Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Risk assessment tools can be used to identify and rank parameters (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. For an illustrative example, see Appendix 2. The initial list of potential parameters can be quite extensive, but can be modified and prioritized by further studies (e.g., through a combination of design of experiments, mechanistic models). The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

2.4 Design Space

The relationship between the process inputs (material attributes and process parameters) and the critical quality attributes can be described in the design space (see examples in Appendix 2).

2.4.1 Selection of Variables

The risk assessment and process development experiments described in Section 2.3 can lead to an understanding of the linkage and effect of process parameters and material attributes on product CQAs, and also help identify the variables and their ranges within which consistent quality can be achieved. These process parameters and material attributes can thus be selected for inclusion in the design space.

A description should be provided in the application of the process parameters and material attributes considered for the design space, those that were included, and their effect on product quality. The rationale for inclusion in the design space should be presented. In some cases it is helpful to provide also the rationale as to why some parameters were excluded. Knowledge gained from studies should be described in the submission. Process parameters and material attributes that were not varied through development should be highlighted.

2.4.2 Describing a Design Space in a Submission

A design space can be described in terms of ranges of material attributes and process parameters, or through more complex mathematical relationships. It is possible to describe a design space as a time dependent function (e.g., temperature and pressure cycle of a lyophilisation cycle), or as a combination of variables such as components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can contribute to the establishment of a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality.

Examples of different potential approaches to presentation of a design space are presented in Appendix 2.

2.4.3 Unit Operation Design Space(s)

The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design space that spans multiple operations. While a separate design space for each unit operation is often simpler to develop, a design space that spans the entire process can provide more operational flexibility. For example, in the case of a drug product that undergoes degradation in solution before lyophilisation, the design space to control the extent of degradation (e.g., concentration, time, temperature) could be expressed for each unit operation or as a sum over all unit operations.

2.4.4 Relationship of Design Space to Scale and Equipment

When describing a design space, the applicant should consider the type of operational flexibility desired. A design space can be developed at any scale. The applicant should justify the relevance of a design space developed at small or pilot scale to the proposed production scale manufacturing process and discuss the potential risks in the scale-up operation.

If the applicant proposes the design space to be applicable to multiple operational scales, the design space should be described in terms of relevant scale-independent parameters. For example, if a product was determined to be shear sensitive in a mixing operation, the design space could include shear rate, rather than agitation rate. Dimensionless numbers and/or models for scaling can be included as part of the design space description.

2.4.5 Design Space Versus Proven Acceptable Ranges

A combination of proven acceptable ranges[1] does not constitute a design space. However, proven acceptable ranges based on univariate experimentation can provide useful knowledge about the process.

2.4.6 Design Space and Edge of Failure

It can be helpful to determine the edge of failure for process parameters or material attributes, beyond which the relevant quality attributes cannot be met. However, determining the edge of failure or demonstrating failure modes are not essential parts of establishing a design space.

2.5 Control Strategy

A control strategy is designed to ensure that a product of required quality will be produced consistently. The elements of the control strategy discussed in Section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), intermediates (in-process materials), container closure system, and drug products contribute to the final product quality. These controls should be based on product, formulation and process understanding and should include, at a minimum, control of the critical process parameters[1] and material attributes.

A comprehensive pharmaceutical development approach will generate process and product understanding and identify sources of variability. Sources of variability that can impact product quality should be identified, appropriately understood, and subsequently controlled. Understanding sources of variability and their impact on downstream processes or processing, in-process materials, and drug product quality can provide an opportunity to shift controls upstream and minimise the need for end product testing. Product and process understanding, in combination with quality risk management (see ICH Q9), will support the control of the process such that the variability (e.g., of raw materials) can be compensated for in an adaptable manner to deliver consistent product quality.

This process understanding can enable an alternative manufacturing paradigm where the variability of input materials could be less tightly constrained. Instead it can be possible to design an adaptive process step (a step that is responsive to the input materials) with appropriate process control to ensure consistent product quality.

Enhanced understanding of product performance can justify the use of alternative approaches to determine that the material is meeting its quality attributes. The use of such alternatives could support real time release testing. For example, disintegration could serve as a surrogate for dissolution for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process (e.g., using

[1] See glossary

weight variation coupled with near infrared (NIR) assay) can enable real time release testing and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards. Real time release testing can replace end product testing, but does not replace the review and quality control steps called for under GMP to release the batch.

A control strategy can include, but is not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- In-process or real-time release testing in lieu of end-product testing (e.g. measurement and control of CQAs during processing);
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing, whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.

Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B.

2.6 Product Lifecycle Management and Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (see ICH Q10).

Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model's performance. The model maintenance is an example of activity that can be managed within a company's own internal quality system provided the design space is unchanged.

Expansion, reduction or redefinition of the design space could be desired upon gaining additional process knowledge. Change of design space is subject to regional requirements.

3. SUBMISSION OF PHARMACEUTICAL DEVELOPMENT AND RELATED INFORMATION IN COMMON TECHNICAL DOCUMENTS (CTD) FORMAT

Pharmaceutical development information is submitted in Section P.2 of the CTD. Other information resulting from pharmaceutical development studies could be accommodated by the CTD format in a number of different ways and some specific

suggestions are provided below. However, the applicant should clearly indicate where the different information is located. In addition to what is submitted in the application, certain aspects (e.g., product lifecycle management, continual improvement) of this guideline are handled under the applicant's pharmaceutical quality system (see ICH Q10).

3.1 Quality Risk Management and Product and Process Development

Quality risk management can be used at different stages during product and process development and manufacturing implementation. The assessments used to guide and justify development decisions can be included in the relevant sections of P.2. For example, risk analyses and functional relationships linking material attributes and process parameters to product CQAs can be included in P.2.1, P.2.2, and P.2.3. Risk analyses linking the design of the manufacturing process to product quality can be included in P.2.3.

3.2 Design Space

As an element of the proposed manufacturing process, the design space(s) can be described in the section of the application that includes the description of the manufacturing process and process controls (P.3.3). If appropriate, additional information can be provided in the section of the application that addresses the controls of critical steps and intermediates (P.3.4). The product and manufacturing process development sections of the application (P.2.1, P.2.2, and P.2.3) are appropriate places to summarise and describe product and process development studies that provide the basis for the design space(s). The relationship of the design space(s) to the overall control strategy can be discussed in the section of the application that includes the justification of the drug product specification (P.5.6).

3.3 Control Strategy

The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarise the overall drug product control strategy. However, detailed information about input material controls and process controls should still be provided in the appropriate CTD format sections (e.g., drug substance section (S), control of excipients (P.4), description of manufacturing process and process controls (P.3.3), controls of critical steps and intermediates (P.3.4)).

3.4 Drug Substance Related Information

If drug substance CQAs have the potential to affect the CQAs or manufacturing process of the drug product, some discussion of drug substance CQAs can be appropriate in the pharmaceutical development section of the application (e.g., P.2.1).

4. GLOSSARY

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Critical Quality Attribute (CQA):

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8).

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation (ICH Q8).

Proven Acceptable Range:

A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

Quality:

The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH Q6A).

Quality by Design (QbD):

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Quality Target Product Profile (QTPP):

A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

Real Time Release Testing:

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls.

Appendix 1. Differing Approaches to Pharmaceutical Development

The following table has been developed to illustrate some potential contrasts between what might be considered a minimal approach and an enhanced, quality by design approach regarding different aspects of pharmaceutical development and lifecycle management. The comparisons are shown merely to aid in the understanding of a range of potential approaches to pharmaceutical development and should not be considered to be all-encompassing. The table is not intended to specifically define the only approach a company could choose to follow. In the enhanced approach, establishing a design space or using real time release testing is not necesserily expected. Current practices in the pharmaceutical industry vary and typically lie between the two approaches presented in the table.

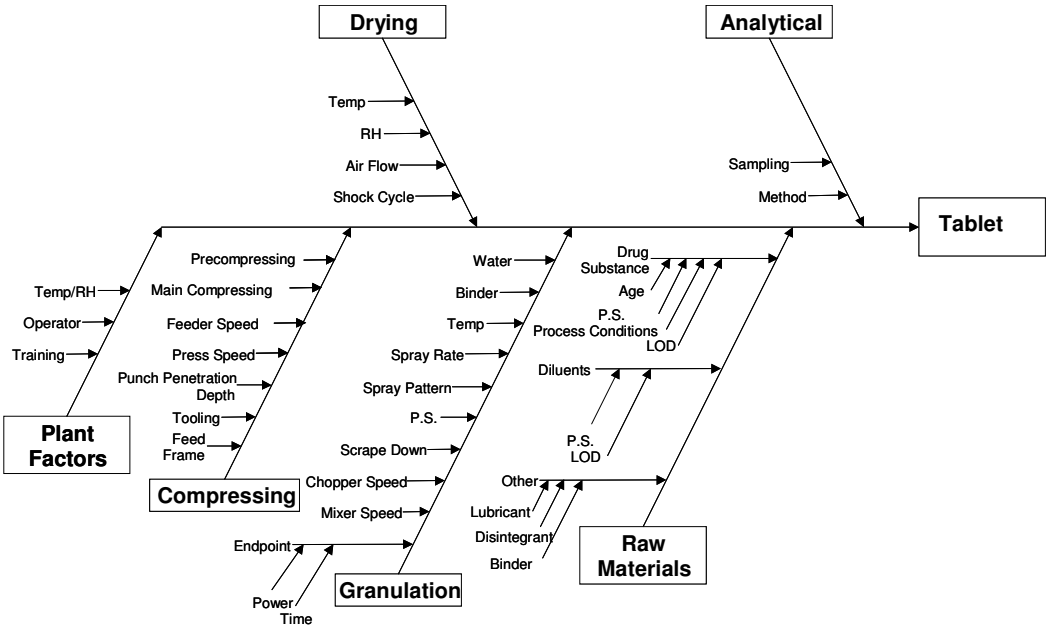
Aspect	Minimal Approaches	Enhanced, Quality by Design Approaches
Overall Pharmaceutical Development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilised
Manufacturing Process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimisation and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process Controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilised with appropriate feed forward and feedback controls • Process operations tracked and trended to support continual improvement efforts post-approval
Product Specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control Strategy	• Drug product quality controlled primarily by intermediates (in-process materials) and end product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release testing or reduced end-product testing
Lifecycle Management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

Appendix 2. Illustrative Examples

A. Use of a risk assessment tool.

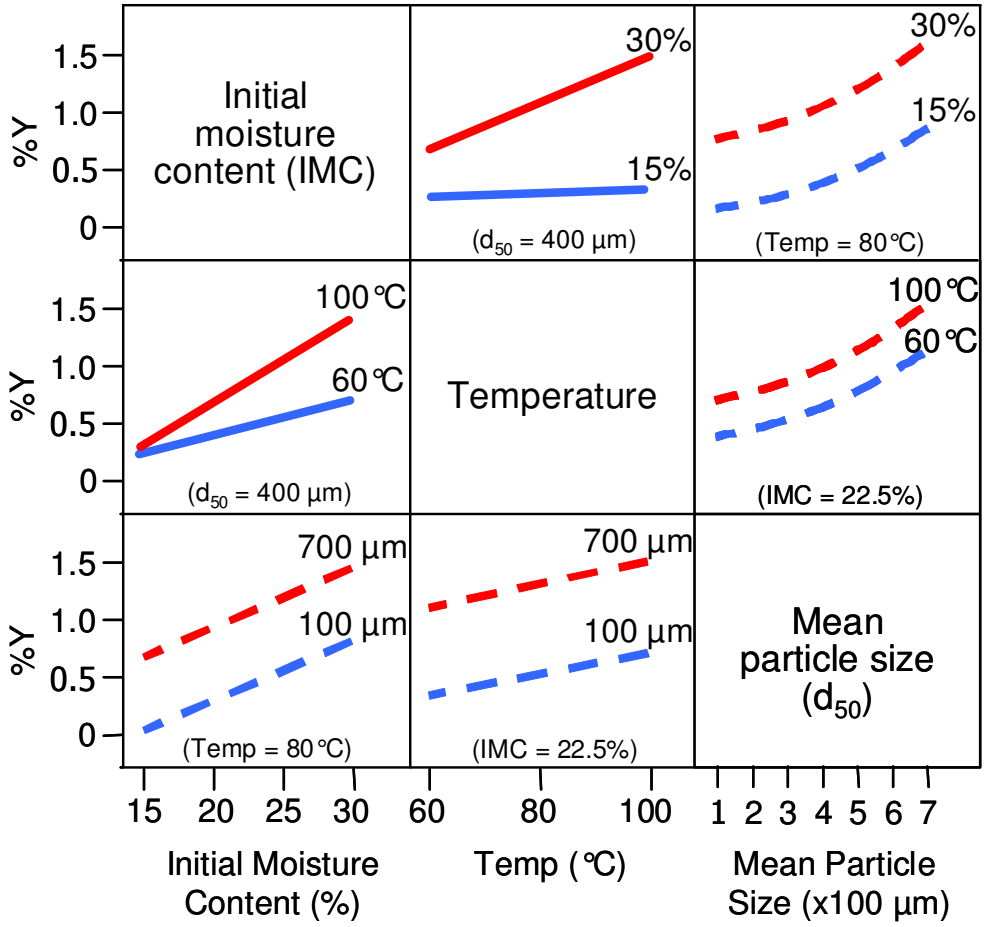
For example, a cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies potential variables which can have an impact on the desired quality attribute. The team could then rank the variables based on probability, severity, and detectability using failure mode effects analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.

Ishikawa Diagram



B. Depiction of interactions

The figure below depicts the presence or absence of interactions among three process parameters on the level of degradation product Y. The figure shows a series of two-dimensional plots showing the effect of interactions among three process parameters (initial moisture content, temperature, mean particle size) of the drying operation of a granulate (drug product intermediate) on degradation product Y. The relative slopes of the lines or curves within a plot indicate if interaction is present. In this example, initial moisture content and temperature are interacting; but initial moisture content and mean particle size are not, nor are temperature and mean particle size.



C. Presentations of design space

Example 1: Response graphs for dissolution are depicted as a surface plot (Figure 1a) and a contour plot (Figure 1b). Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size.)

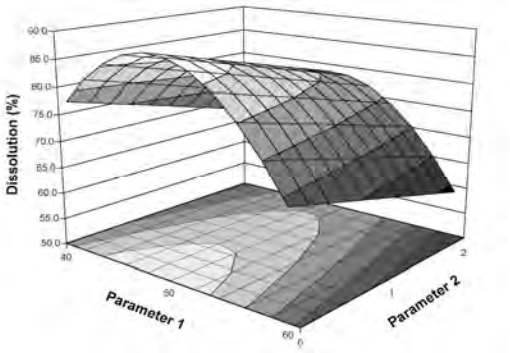


Figure 1a: Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.

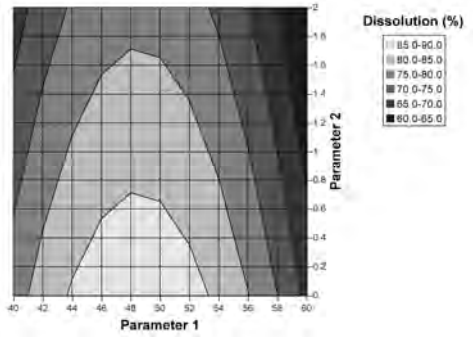


Figure 1b: Contour plot of dissolution from example 1a.

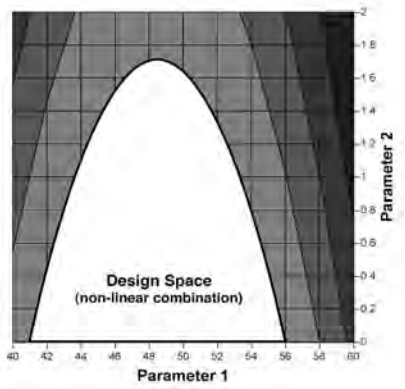


Figure 1c: Design space for granulation parameters, defined by a non-linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

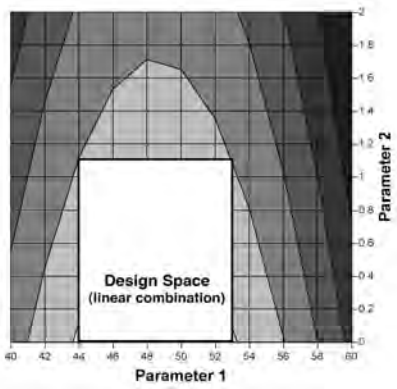


Figure 1d: Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%).

Two examples are given of potential design spaces. In Figure 1c, the design space is defined by a non-linear combination of parameter ranges that delivers the dissolution critical quality attribute. In this example, the design space is expressed by the response surface equation resolved at the limit for satisfactory response (i.e.,80% dissolution). The acceptable range of one parameter is dependent on the value of the other. For example:

- *If Parameter 1 has a value of 46, then Parameter 2 has a range of 0 and 1.5*
- *If Parameter 2 has a value of 0.8, then Parameter 1 has a range of 43 and 54*

The approach in Figure 1c allows the maximum range of operation to achieve the desired dissolution rate. In Figure 1d, the design space is defined as a smaller range, based on a linear combination of parameters.

- *Parameter 1 has a range of 44 and 53*
- *Parameter 2 has a range of 0 and 1.1*

While the approach in Figure 1d is more limiting, the applicant may prefer it for operational simplicity.

This example discusses only two parameters and thus can readily be presented graphically. When multiple parameters are involved, the design space can be presented for two parameters, in a manner similar to the examples shown above, at different values (e.g., high, middle, low) within the range of the third parameter, the fourth parameter, and so on. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation.

Example 2: Design space determined from the common region of successful operating ranges for multiple CQAs. The relations of two CQAs, i.e., tablet friability and dissolution, to two process parameters of a granulation operation are shown in Figures 2a and 2b. Parameters 1 and 2 are factors of a granulation operation that affect the dissolution rate of a tablet (e.g., excipient attribute, water amount, granule size). Figure 2c shows the overlap of these regions and the maximum ranges of the proposed design space. The applicant can elect to use the entire region as the design space, or some subset thereof.

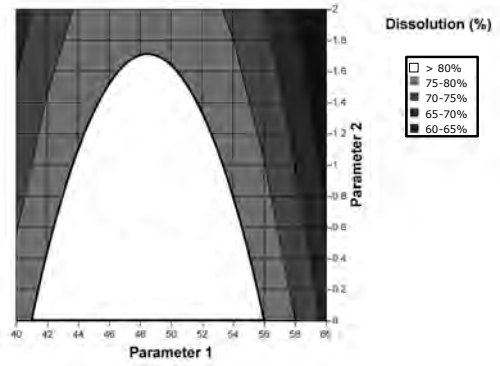


Figure 2a: Contour plot of dissolution as a function of Parameters 1 and 2.

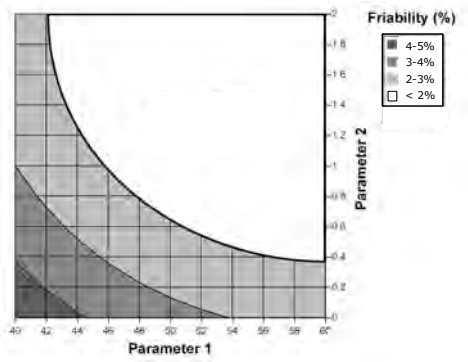


Figure 2b: Contour plot of friability as a function of Parameters 1 and 2.

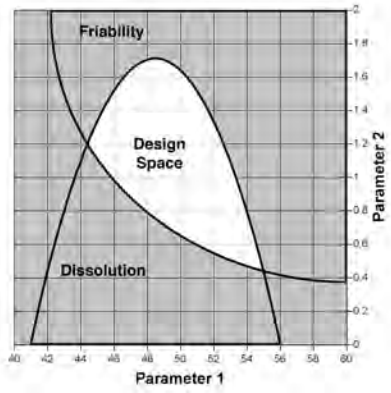


Figure 2c: Proposed design space, comprised of the overlap region of ranges for friability and or dissolution.

Example 3: The design space for a drying operation that is dependent upon the path of temperature and/or pressure over time. The end point for moisture content is 1-2%. Operating above the upper limit of the design space can cause excessive impurity formation, while operating below the lower limit of the design space can result in excessive particle attrition.

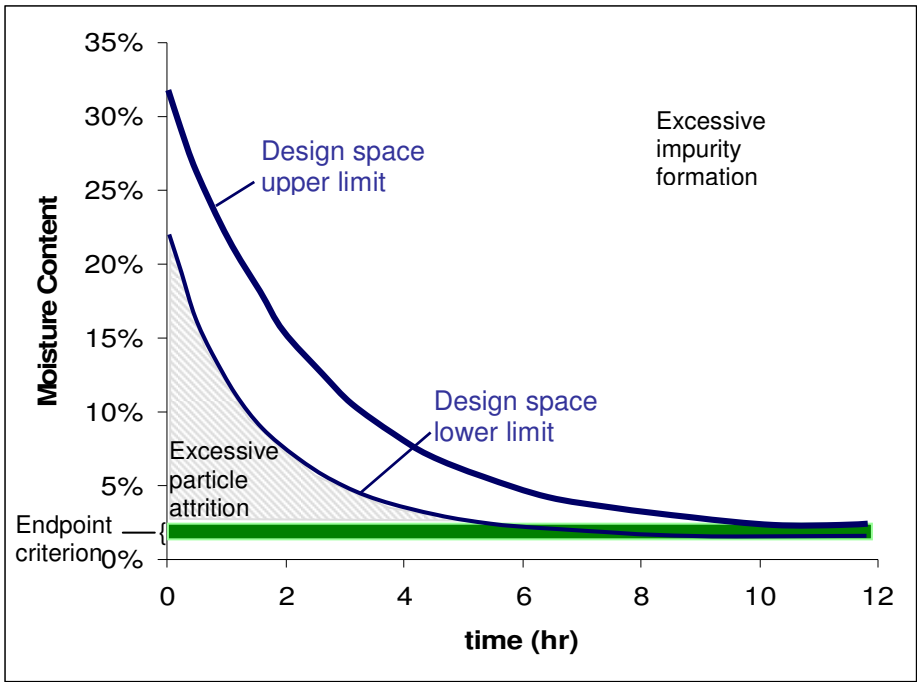


Exhibit 50

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current *Step 4* version
dated 9 November 2005

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q9
Document History

First Codification	History	Date	New Codification **November 2005**
Q9	Approval by the Steering Committee under *Step 2* and release for public consultation.	22 March 2005	Q9
Q9	Approval by the Steering Committee of *Post Step 2* correction	15 June 2005	Q9

Current *Step 4* version

Q9	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	9 November 2005	Q9

QUALITY RISK MANAGEMENT

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 9 November 2005, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

QUALITY RISK MANAGEMENT

1. INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate

industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

2. SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).

3. PRINCIPLES OF QUALITY RISK MANAGEMENT

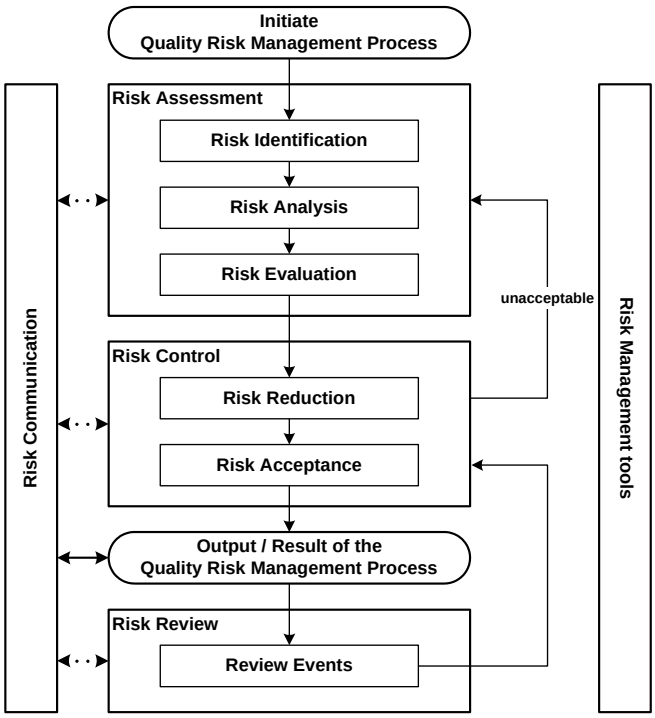
Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4. GENERAL QUALITY RISK MANAGEMENT PROCESS

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision. Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

4.1 Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- assure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.

4.2 Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

4.3 Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high", "medium", or "low", which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4 Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.5 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

4.6 Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

5. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/ or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/ or criticality of the issue to be addressed.

6. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be

used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management.

Examples for industry operations and activities (see Annex II):

- Development;
- Facility, equipment and utilities;
- Materials management;
- Production;
- Laboratory control and stability testing;
- Packaging and labeling.

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities.

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

7. DEFINITIONS

Decision Maker(s):

Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability:

The ability to discover or determine the existence, presence, or fact of a hazard.

Harm:

Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard:

The potential source of harm (ISO/IEC Guide 51).

Product Lifecycle:

All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality:

The degree to which a set of inherent properties of a product, system or process fulfills requirements (see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System:

The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements:

The explicit or implicit needs or expectations of the patients or their surrogates (e.g., health care professionals, regulators and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk:

The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance:

The decision to accept risk (ISO Guide 73).

Risk Analysis:

The estimation of the risk associated with the identified hazards.

Risk Assessment:

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication:

The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control:

Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation:

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification:

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management:

The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk.

Risk Reduction:

Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review:

Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity:

A measure of the possible consequences of a hazard.

Stakeholder:

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend:

A statistical term referring to the direction or rate of change of a variable(s).

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Annex I: Risk Management Methods and Tools

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- Flowcharts;
- Check Sheets;
- Process Mapping;
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram).

I.2 Failure Mode Effects Analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited

to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process;

(2) determine the critical control points;

(3) establish critical limits;

(4) establish a system to monitor the critical control points;

(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;

(6) establish system to verify that the HACCP system is working effectively;

(7) establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

- Control Charts, for example:
  - Acceptance Control Charts (see ISO 7966);
  - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873);
  - Cumulative Sum Charts (see ISO 7871);
  - Shewhart Control Charts (see ISO 8258);
  - Weighted Moving Average.
- Design of Experiments (DOE);
- Histograms;
- Pareto Charts;
- Process Capability Analysis.

Annex II: Potential Applications for Quality Risk Management

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations;

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness);

To identify the training, experience, qualifications and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc;

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- Existing legal requirements;
- Overall compliance status and history of the company or facility;
- Robustness of a company's quality risk management activities;
- Complexity of the site;
- Complexity of the manufacturing process;
- Complexity of the product and its therapeutic significance;
- Number and significance of quality defects (e.g., recall);
- Results of previous audits/inspections;
- Major changes of building, equipment, processes, key personnel;
- Experience with manufacturing of a product (e.g., frequency, volume, number of batches);

- Test results of official control laboratories.

Periodic review

To select, evaluate and interpret trend results of data within the product quality review;

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

Change management / change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing;

To evaluate the impact of the changes on the availability of the final product;

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers;

To determine appropriate actions preceding the implementation of a change, e.g., additional testing, (re)qualification, (re)validation or communication with regulators.

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1);

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings;

To determine the appropriateness and type of post-inspection regulatory follow-up;

To evaluate information submitted by industry including pharmaceutical development information;

To evaluate impact of proposed variations or changes;

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality Risk Management as Part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:

- reduce product and material defects;
- reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;

To make use of the "design space" concept (see ICH Q8).

II.4 Quality Risk Management for Facilities, Equipment and Utilities

Design of facility / equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- flow of material and personnel;
- minimize contamination;
- pest control measures;
- prevention of mix-ups;
- open versus closed equipment;
- clean rooms versus isolator technologies;
- dedicated or segregated facilities / equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water);

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns);

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

Qualification of facility/equipment/utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production);

To determine acceptable (specified) cleaning validation limits.

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules.

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);

To determine the extent of validation, e.g.,

- identification of critical performance parameters;
- selection of the requirements and design;
- code review;
- the extent of testing and test methods;
- reliability of electronic records and signatures.

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);

To determine appropriateness of reprocessing, reworking, use of returned goods.

Storage, logistics and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);

To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;

To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);

To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods;

To determine the extent for follow-up activities (e.g., sampling, monitoring and re-validation);

To distinguish between critical and non-critical process steps to facilitate design of a validation study.

In-process sampling & testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);

To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release.

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest period / expiration date

To evaluate adequacy of storage and testing of intermediates, excipients and starting materials.

II.8 Quality Risk Management as Part of Packaging and Labelling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of container closure system

To determine the critical parameters of the container closure system.

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

Exhibit 51

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2)

Current *Step 4* version

dated 25 October 2006

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Q3A(R2)
Document History

First Codification	History	Date	New Codification **November 2005**
Q3	Approval by the Steering Committee under *Step 2* and release for public consultation.	15 March 1994	Q3A
Q3A	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies. Q3 was renamed Q3A.	30 March 1995	Q3A
Q3A(R)	Approval by the Steering Committee of the first Revision under *Step 2* and release for public consultation.	7 October 1999	Q3A(R1)
Q3A(R)	Approval by the Steering Committee of the first Revision under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	6 February 2002	Q3A(R1)

Current *Step 4* version

Q3A(R2)	Approval by the Steering Committee of the revision of the Attachment 2 directly under *Step 4* without further public consultation.	25 October 2006	Q3A(R2)

IMPURITIES IN NEW DRUG SUBSTANCES

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 7 February 2002, this guideline is recommended for adoption to the three regulatory parties to ICH.

Attachment 2 has been revised on 25 October 2006.

TABLE OF CONTENTS

IMPURITIES IN NEW DRUG SUBSTANCES

1. PREAMBLE

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semi-synthetic products derived therefrom, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from two perspectives:

Chemistry Aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures; and

Safety Aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

2. CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

- Starting materials
- By-products
- Intermediates
- Degradation products
- Reagents, ligands and catalysts

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

- Reagents, ligands and catalysts
- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are

generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are: (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as Good Manufacturing Practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

3. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

3.1 Organic Impurities

The applicant should summarise the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarise the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH Guideline Q1A on Stability) used to identify potential impurities arising during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences discussed.

The studies conducted to characterise the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described. Note that any impurity at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than (≤) the identification thresholds, it is useful also to report the results of these studies.

Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold. All impurities should be qualified as described later in this guideline.

3.2 Inorganic Impurities

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carry-over of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of

inorganic impurities in the new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

3.3 Solvents

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C Guideline for Residual Solvents.

4. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B Guidelines for Analytical Validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds (See Attachment 1) does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be acceptable where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterised according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

5. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as “complies”, “meets limit” etc. Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate

descriptor, e.g., retention time. If a higher reporting threshold is proposed, it should be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.

For each batch of the new drug substance, the report should include:

- Batch identity and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Impurity content, individual and total
- Use of batches
- Reference to analytical procedure used

6. LISTING OF IMPURITIES IN SPECIFICATIONS

The specification for a new drug substance should include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities in the new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities" in this guideline. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in the specification should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Specified, unidentified impurities should be referred to by an appropriate qualitative analytical descriptive label (e.g., “unidentified A", “unidentified with relative retention of 0.9”). A general acceptance

criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by safety data, and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of the new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A Guideline on Specifications, Decision Tree #1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds (See Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified impurities and total impurities.

In summary, the new drug substance specification should include, where applicable, the following list of impurities:

Organic Impurities

- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Residual Solvents

Inorganic Impurities

7. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in Attachment 1 are exceeded.

Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially

important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification" (Attachment 3) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process. Any new impurity observed in later stages of development should be identified if its level is greater than (>) the identification threshold given in Attachment 1 (see the "Decision Tree for Identification and Qualification" in Attachment 3). Similarly, the qualification of the impurity should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.

8. GLOSSARY

Chemical Development Studies: Studies conducted to scale-up, optimise, and validate the manufacturing process for a new drug substance.

Enantiomeric Impurity: A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a non-superimposable mirror image.

Extraneous Contaminant: An impurity arising from any source extraneous to the manufacturing process.

Herbal Products: Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present.

Identified Impurity: An impurity for which a structural characterisation has been achieved.

Identification Threshold: A limit above (>) which an impurity should be identified.

Impurity: Any component of the new drug substance that is not the chemical entity defined as the new drug substance.

Impurity Profile: A description of the identified and unidentified impurities present in a new drug substance.

Intermediate: A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance.

Ligand: An agent with a strong affinity to a metal ion.

New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphic Forms: Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudo-polymorphs) and amorphous forms.

Potential Impurity: An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.

Qualification: The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification Threshold: A limit above (>) which an impurity should be qualified.

Reagent: A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a new drug substance.

Reporting Threshold: A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B.

Solvent: An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified Impurity: An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

Starting Material: A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Unidentified Impurity: An impurity for which a structural characterisation has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified impurity: An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification.

ATTACHMENT 1
Thresholds

Maximum Daily Dose[1]	**Reporting Threshold**[2,3]	**Identification Threshold**[3]	**Qualification Threshold**[3]
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

[1] The amount of drug substance administered per day

[2] Higher reporting thresholds should be scientifically justified

[3] Lower thresholds can be appropriate if the impurity is unusually toxic

ATTACHMENT 2

Illustration of Reporting Impurity Results for Identification and Qualification in an Application

The attachment is only illustrative and is not intended to serve as template how results on impurities should be presented in an application file. Normally raw data are not presented.

Example 1: 0.5 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 0.15% exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[1)]	0.6	Yes	None[1)]
0.1649	0.16[1)]	0.8	Yes	Yes[1)]

Example 2: 0.8 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

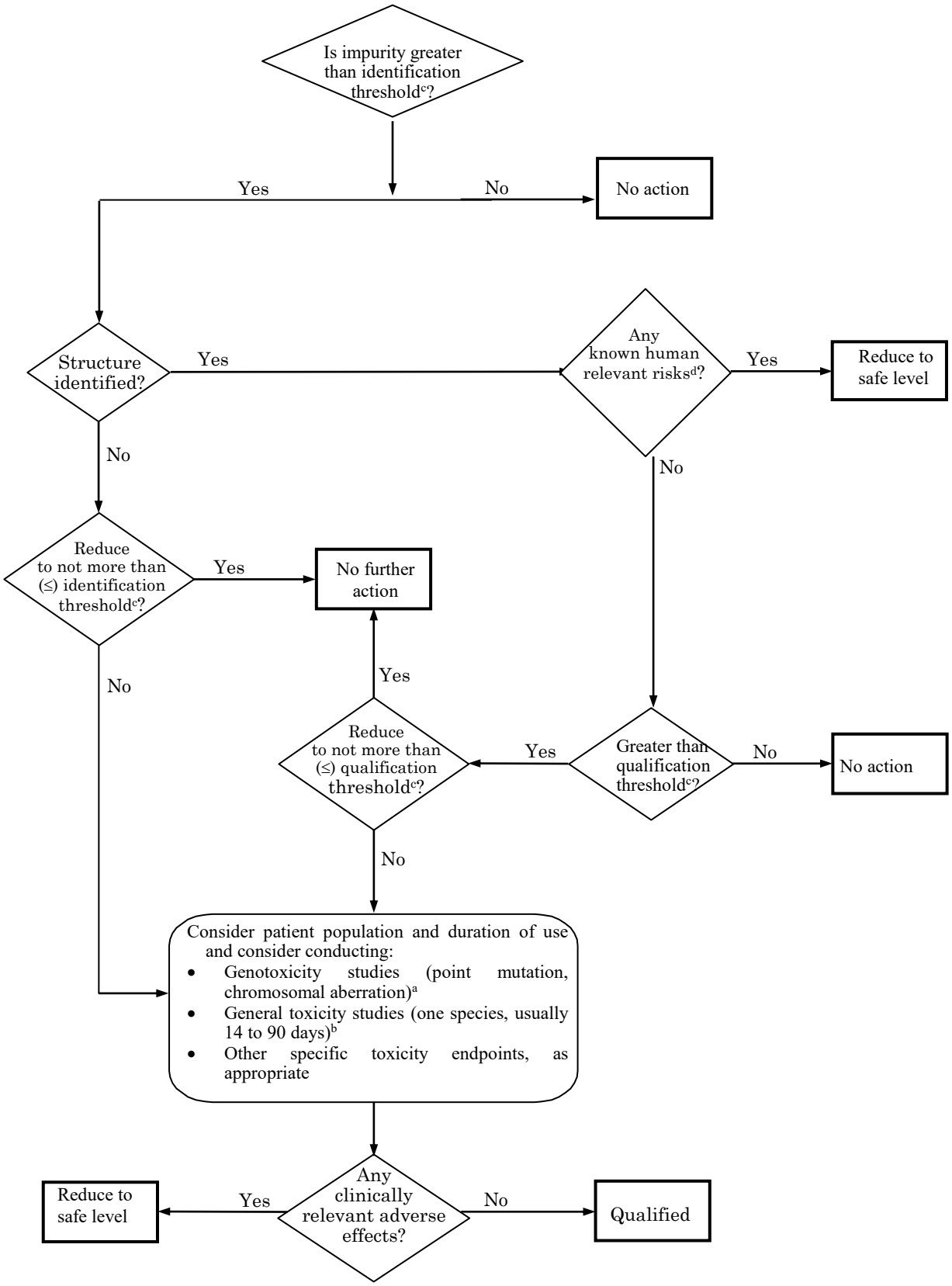
"Raw" Result (%)	Reported Result (%) Reporting threshold =0.05%	Calculated Total Daily Intake (TDI) (mg) of the impurity (rounded result in mg)	Action	
			Identification (Threshold 0.10% exceeded?)	Qualification (Threshold 1.0 mg TDI exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	yes	None[1)2)]
0.143	0.14	1.1	yes	Yes[1)]

1) After identification, if the response factor is determined to differ significantly from the original assumptions, it may be appropriate to re-measure the actual amount of the impurity present and re-evaluate against the qualification threshold (see Attachment 1).

2) To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: when the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold and compared to the threshold. For example the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount) which is then rounded up to 1.0 mg; so the qualification threshold expressed in TDI (1.0 mg) is not exceeded.

ATTACHMENT 3

Decision Tree for Identification and Qualification



Notes on Attachment 3

a) If considered desirable, a minimum screen (e.g., genotoxic potential), should be conducted.
A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

b) If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximise the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

c) Lower thresholds can be appropriate if the impurity is unusually toxic.

d) For example, do known safety data for this impurity or its structural class preclude human exposure at the concentration present?

Exhibit 53

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	MDL No. 2875

EXPERT REPORT OF DAVID L. CHESNEY, MSJ

done to minimize the potential for undue influence or conflict of interest in Quality Unit decision-making, preserving the integrity of the unit's final authority contemplated in 21 CFR § 211.22. Even though the regulations are not prescriptive on this point, organizational independence of the Quality Unit is a widely followed practice in the pharmaceutical industry.

E. GMP as Applied to Active Pharmaceutical Ingredients (API)

API meet the definition of a "drug" in the FDCA[21], which does not distinguish between API and finished drug products. Therefore, the requirement to comply with GMP applies to API at the statutory level[22]. However, the GMP regulations at 21 CFR Part 211 are binding only for finished drug products. There are currently no FDA regulations specifying what constitutes GMP for API.

In Compliance Program 7356.002F, "Active Pharmaceutical Ingredient (API) Process Inspection"[23], FDA states in part:

> APIs are subject to the adulteration provisions of Section 501(a)(2)(B) of the Act, which requires all drugs to be manufactured in conformance with CGMP. No distinction is made between an API and a finished pharmaceutical in the Act and the failure of either to comply with CGMP constitutes a violation of the Act. FDA has not promulgated CGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals). Thus, the use of "CGMP" in this document refers to the requirements of the Act rather than the requirements of 21 CFR Parts 210 and 211 regulations for finished pharmaceuticals.
>
> FDA has long recognized that the CGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable **in concept** to Active Pharmaceutical Ingredient (API) manufacturing. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing adequate written procedures and controls designed to assure manufacturing processes and controls

[21] 21 USC § 321(g).
[22] 21 USC § 351(a)(2)(B).
[23] Current version dated September 11, 2015.

> are valid, establishing a system of in-process material and final drug tests, and ensuring stability of drugs for their intended period of use. In 2001, FDA adopted an internationally harmonized guidance to industry on API CGMPs in conjunction with regulatory partners in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is ICH Q7A[24], Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients. ICH Q7A represents the Food and Drug Administration's (FDA's) current thinking on CGMPs for API's. Thus, API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory CGMP requirement. However, **alternate approaches may be used** if such approaches satisfy the requirements of Section 501(a)(2)(B) of the Act as long as the approach ensure that the API meets its purported or represented purity, identity, and quality characteristics. (emphasis supplied)

The lack of a binding regulation increases the need for the FDA to carefully balance scientific, legal and policy factors in each case in order to reach a defensible position about the significance of GMP inspection observations that arise in an API manufacturing context.

V. GMP Compliance Status of Zhejiang Huahai Pharmaceutical Co. Ltd.

The opinions expressed herein are based solely upon review of documents as listed in Exhibit B of this declaration. At no time did I personally visit any ZHP location, nor did I interview any ZHP staff. The time period to which the opinions expressed herein apply are from approximately August of 2013 until October of 2019 unless otherwise stated.

At the conclusion of an FDA inspection, the FDA-483 is issued to top management (if there are observations). Subsequently, the FDA employee(s) conducting the inspection prepare an Establishment Inspection Report (EIR) expanding upon the findings on the 483, and supporting those findings with evidence obtained during the inspection. Other sections of the EIR develop evidence of individual (personal) responsibility for the observations, and include other ancillary

[24] Renumbered as "Q7" since the issue date of this FDA reference.

Exhibit 54

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

****

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION

MDL No. 2875

****

HON ROBERT B. KUGLER

THIS DOCUMENT APPLIES TO ALL CASES

****

- CONFIDENTIAL INFORMATION -
SUBJECT TO PROTECTIVE ORDER

Remote Videotaped Deposition of DAVID L. CHESNEY, commencing at 9:40 a.m., on the 21st of March, 2022, before Maureen O'Connor Pollard, Registered Diplomate Reporter, Realtime Systems Administrator, Certified Shorthand Reporter.

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Direction to Witness Not to Answer
PAGE LINE
None.

Request for Production of Documents
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None.

Stipulations
PAGE LINE
None.

Questions Marked Highly Confidential
PAGE LINE
None.

P R O C E E D I N G S

THE VIDEOGRAPHER: We are now recording and on the record. My name is David Stone. I'm a legal video specialist on behalf of Golkow Litigation Services.

Today's date is March 21st, and the time is 9:40 a.m.

This is the deposition of David Chesney in the matter of In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation, plaintiffs, versus -- in the United States District Court, District of New Jersey, Case Number, MDL Number 2875.

This deposition is being taken via remote recording on behalf of the plaintiffs.

The court reporter is Maureen Pollard.

Counsel will state their appearances, and the court reporter will administer the oath.

MR. SLATER: Adam Slater, Chris Gaddis, Julia Slater for plaintiffs.

MR. FOX: Thomas Fox, Skadden, Arps, for the ZHP defendants.

///

DAVID L. CHESNEY,

having been duly remotely identified and sworn, was examined and testified as follows:

EXAMINATION

BY MR. SLATER:

Q. Good morning, Mr. Chesney.

A. Good morning.

MR. FOX: Adam, I just want to make clear, this is being taken pursuant to the remote deposition protocol in the case?

MR. SLATER: I think that we have a remote deposition protocol.

MR. FOX: Yes.

MR. SLATER: Why are you asking me that?

MR. FOX: I just wanted to make sure, that's all.

MR. SLATER: I just have never

been asked that question before in one of depositions we were doing remotely. I thought it was a trick question. I think so.

BY MR. SLATER:

Q. Okay. Good morning, Mr. Chesney.

A. Good morning.

Q. We're going to take your deposition now. You understand that, right?

A. I do.

Q. Have you been deposed before?

A. Yes.

Q. How many times?

A. Let's see. Four or five times, I guess.

Q. You understand you're under oath and must tell the truth, right?

A. Yes.

Q. If I ask you a question that for some reason you don't feel you can answer truthfully and completely, for any reason, just tell me. It may be that I mispronounce a word, or ask you a question that

technically doesn't make sense to you because I don't understand something either from a regulatory perspective or legal perspective, whatever it may be, for any reason you're not clear on my question or don't feel like you can answer it, just tell me and we'll try to figure out what I need to clarify, and I'll try to do that. Okay?

A. Okay.

Q. Counsel may object. I think it would be unlikely he won't object during the course of the deposition. That's routine. It's never to signal an answer or how to answer, it's just preserving rights -- or at least it should never be to signal an answer, and I doubt it would be today, and I would expect it wouldn't be.

In any event, let your counsel object, and then answer the question, unless he tells you not to. Okay?

A. Yes, sir.

MR. SLATER: Chris, let's put up the deposition notice as Exhibit 1.

///

(Whereupon, Chesney Exhibit Number 1 was marked for identification.)

BY MR. SLATER:

Q. Mr. Chesney, this is the deposition notice we served for your deposition.

Have you seen this document before?

A. Yes.

Q. Did you read it and go through all the requests?

A. Yes.

Q. Did you provide any documents to the lawyers that retained you in this case to be provided to us pursuant to this deposition notice?

A. Before I received the notice I did, yes.

Q. Okay. Once you got the notice, was there anything else that you identified and provided to counsel?

A. I don't recall that I did, no.

Q. When you say you don't recall,

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you don't recall if that happened, or you don't -- I'm unclear on your answer.
A. We had a discussion. The list of requests was quite broad, and I had difficulty interpreting the scope of some of the requests, and we discussed that.
At the end of that discussion, I believe counsel was going to submit a response, and I never heard anything further after that.
Q. At the end of that discussion when counsel worked through what the deposition notice was asking for, was there any information or documents that you provided to counsel to be provided to us?
A. No.
MR. SLATER: Okay. Let's take that document down, and put up as Exhibit 2 the response to the deposition notice, please.
(Whereupon, Chesney Exhibit Number 2 was marked for identification.)
///

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BY MR. SLATER:
Q. On the screen as Exhibit 2 is what we were provided as the response to our deposition notice. Have you seen that document?
A. No.
Q. One of the things we requested from you was the invoices in this matter.
MR. SLATER: And I guess, Chris, let's go to the invoices as Exhibit 3, and then we'll come back to the dep notice after, if that's possible.
(Whereupon, Chesney Exhibit Number 3 was marked for identification.)
MR. SLATER: Perfect. Thank you.
BY MR. SLATER:
Q. On the screen as Exhibit 3 are the invoices we were provided, and it shows that you began to work in this matter in June of 2021, is that correct?
A. That's correct.

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Q. Who contacted you and asked you to get involved in this case?
A. Frederick Ball of Duane Morris.
Q. Did you know Mr. Ball before he contacted you in June of 2021?
A. No.
Q. You'd never met him before?
A. I had not.
Q. Do you know how it was that he came to contact you? Did he tell you why he contacted you?
A. I don't recall. He probably told me at the time, but I don't recall now where he got my name.
Q. The response to the deposition notice, which we don't have to pull up, says that the invoices that were provided were in connection with the preparation of your expert report and your related testimony in this litigation. Is that what these invoices represent?
A. Yes. The majority of the time was the preparation of the expert report and the work I did researching information in

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that preparation.
Q. Other than writing this report and preparing for this deposition, have you done any other work for ZHP or any of its subsidiaries in connection with the nitrosamine contamination of its valsartan?
A. No.
Q. Have you been asked to consult or provide any opinions with regard to any disputes that ZHP may be having with any of its customers?
A. No.
Q. Okay. I added up these invoices which are dated between June 2021 and January of 2022 at $51,000.
Does that sound correct?
A. I think it's a little on the low side. I had added them up, and I think I came up with around 56.
Q. Okay. These invoices are up through January of 2022, the last one being $13,000.
MR. SLATER: Maybe we can go to that one, Chris, the last page.

Perfect.
Q. Looking at the last page of this group of invoices, this is from January of 2022, $13,000, correct?
A. Yes.
Q. What amount of time have you spent since January up until today in connection with this matter?
A. I have that information on my time sheet records, but I don't have it with me. It's approximately 25 hours, more or less.
Q. Does that include your preparation right up until the point when we started the deposition?
A. I don't believe it includes the hours I spent this weekend looking over my report, but it's pretty close. It might be between 25 and 30.
Q. So 25 hours approximately before the weekend, and then maybe another five or so hours over the weekend before today's deposition?
A. Approximately, yes.

Q. Okay. Thank you.
MR. SLATER: All right. Chris, let's go back to the deposition notice, if we could, please. Not the notice, I'm sorry, I meant the response. My bad. Thank you.
Q. I'm not going to go through all these requests, and you haven't read the responses, so I'm not going to go through that with you today in great detail. But what I would like to ask you is --
MR. SLATER: Let's go to request number 8. That's the -- go to the responses and objections to the requests, number 8. Perfect. Thanks, Chris.
Q. Looking at number 8, which we asked for any documentation of any research that you had performed with regard to the FDA's regulation of API and finished drug products, FDA inspections, current good manufacturing processes, and the risks and benefits of any angiotensin II receptor blockers or nitrosamines, we were told that

you had worked at the FDA for 23 years, and have had an FDA-related consulting practice for more than a quarter of a century, and in those roles you'd informally researched countless issues over the course of your career, and that you have already submitted a list of your publications, and not conducted academic research regarding the list of topics. That was the response we were given. You can see that there.
Do you see that?
A. Yes.
Q. I just want to know talking to you now, have you in connection with this work -- well, rephrase.
Have you ever done any research regarding nitrosamines?
A. No.
Q. And that's true right up until right now?
A. Other than just briefing myself on the general issue and rereading some of the press that was out when it was made public and that sort of thing. No, no

technical research.
Q. I think I saw in a few places in your report where you said you'd defer to scientific or to others with scientific expertise.
Is this one of the areas where you would defer to others with scientific expertise, meaning the nitrosamines and the risks posed by nitrosamines?
A. Yes.
MR. FOX: Objection to form.
Just make sure you slow down, David, so you give me an opportunity to make an objection on the record.
BY MR. SLATER:
Q. I'll just ask it again just because counsel objected, it may be that I talked too much in my question, happens from time to time.
Am I correct that you'd defer to other experts regarding the risks posed by nitrosamines as relevant in this case?
A. Yes.
Q. When I asked you if you'd defer

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to others, I didn't see you specifically cite any of their expert reports, you're just saying in general you would defer to others who have that expertise, is that correct?
MR. FOX: Objection to the form.
A. Yes.
BY MR. SLATER:
Q. Am I correct that in your experience both with the FDA and as a consultant following the time you left the FDA, you've never been involved in a matter that involved potential nitrosamine impurities in either an API or a finished dose product?
A. That's correct.
Q. Is this the first time in your career you've been involved in a matter where nitrosamines were a relevant factor in the analysis you were providing, meaning one of the constituent variables in the case was nitrosamines?
MR. FOX: Objection to form.
A. Yes.

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BY MR. SLATER:
Q. Before you were retained in this case, had you ever heard of NDMA?
A. Yes.
Q. And how did you know what NDMA was?
A. There were press reports involving the occurrence of NDMA in a variety of products, some gastrointestinal products as well as the valsartan-irbesartan family, and I read those press reports in the literature.
Q. Other than seeing press reports regarding the recent discovery of NDMA in various drug products, had you ever had any occasion to know what NDMA was before that?
A. No.
MR. FOX: Objection to form. Slow down, David.
BY MR. SLATER:
Q. I didn't see any discussion of NDEA in your report. Is that something you did not address at all in your report?
A. I did not address it.

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Q. I also saw no discussion of the TEA process for manufacture of valsartan API at ZHP. Am I also correct that is not something that you addressed at all in your report?
A. You're correct.
MR. SLATER: Let's take those down and go to Mr. Chesney's report. We'll mark that as Exhibit 3, along with the attached Exhibits A and B.
(Whereupon, Chesney Exhibit Number 4 was marked for identification.)
BY MR. SLATER:
Q. Mr. Chesney, you have in front of you on the screen your report which we've marked as Exhibit 3. I understand you're not scrolling right through it, but does that look like the first page of your report?
A. Yes.
Q. And I can tell you --
MR. GEDDIS: Adam, for the record it's Exhibit 4.
MR. SLATER: Did I say 3? I

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meant 4. Sorry about that. Let me rephrase.
BY MR. SLATER:
Q. Mr. Chesney, on the screen as Exhibit 4 we have your report. Does that look like your report right there?
A. Yes.
Q. And I have it as 59 pages, and then there's a digital signature for you on, it looks like, January 12, 2022. Is that when you put your signature on it and stamped this as a final report?
A. I'm not looking at it, but that sounds right.
Q. Do you have your report there in hard copy?
A. I do. I was just trying to flip to that page.
Q. Go ahead, take a look, and we'll just make sure we're on the same page of that.
MR. SLATER: You don't have to scroll to that, I don't think, Chris, because he has it.

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A. Yes, it was digitally signed on January 12th, that's correct.
Q. And that was the day when you finalized and confirmed your opinions in this case?
A. Yes.
Q. Does this report contain each of the opinions you formed in this matter?
A. Yes.
Q. You went through a number of facts and discussed a number of facts in the course of your report. Were those the facts that you felt were most important to you in supporting or formulating your opinions?
A. Yes.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. I'm just going to digress for a second. We can leave that on the screen. I just want to ask you a few background questions.
Can you tell me how many times you've been retained as an expert witness in civil litigation?

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A. Four or five times.
Q. What is the bulk of the work you have done as a consultant since you left the FDA? It sounds like it's not litigation-based, so I'm curious what it is that you generally do.
A. I provide advice to clients on compliance strategy. I help them respond to FDA findings when they have inspections. I help them prepare for and manage FDA inspections. I conduct audits from time to time, some of which are general audits for compliance purposes, others of which are intended as mock FDA inspections to help them prepare for the real event. Any of a variety of other ad hoc issues that arise with clients that involve FDA compliance matters.
Q. Have you ever done any work in the past for ZHP, Prinston, Solco, or Huahai US?
A. No.
Q. Have you done any work for any of the other manufacturers or parties to this litigation, to your knowledge?

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A. The only two I recall seeing the names of are Teva and Mylan, and the answer in both cases is no.
Q. How about Aurobindo?
A. No.
Q. Hetero?
A. No.
Q. How about Torrent?
A. No.
Q. When you were an FDA investigator -- rephrase.
When you worked at the FDA, did your responsibilities include evaluation of manufacturers to determine whether there were GMP violations in the manufacture of API?
A. Yes.
Q. Same question with regard to manufacture of finished dose products.
A. Yes.
Q. In your work at the FDA, how much of your work was focused on that area, evaluation of potential GMP violations in the manufacture of API or finished dose?
A. I can't quantitate that

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precisely for you.
Q. Can you give me some idea of how many matters you investigated where that was the question?
MR. FOX: Objection to form.
A. Almost impossible, sir. I began my FDA career in 1972. Between that and my consulting career, I've spent nearly 50 years. It's very difficult to say how many of these issues I've dealt with over an extensive period of time like that.
BY MR. SLATER:
Q. So -- and I'm not going to push it. If you're not able to estimate the number of times that you addressed that issue at the FDA, I'll let it go if you tell me that.
A. I could not give you an estimate I would be confident about.
Q. Looking at your report, let me just find a good jumping off point.
MR. SLATER: Let's go to page 11, if we could, please, Chris.
Q. I was curious, on page 11 --

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rephrase.
On page 11 there's a heading "FDA Awards and Recognition" --
A. Yes.
Q. -- that says, "In 1990, I received the FDA Award of Merit, the FDA's highest award for individual achievement, for my work coordinating a major investigation involving deliberate contamination of imported produce sent to the United States."
When you say "deliberate contamination," what was that referring to? What happened?
A. Injection of grapes from a country of Chile with cyanide residues.
Q. I suppose you would agree with me that the deliberate contamination of a product regulated by the FDA would be a significant violation?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. Would you agree that the deliberate contamination of a product

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regulated by the FDA would be a GMP violation?
MR. FOX: Objection to form.
A. It depends.
BY MR. SLATER:
Q. Well, in this case where somebody injected cyanide into grapes, was that a GMP violation?
A. No.
Q. What was it a violation of?
A. Title 18 US Code Section 1365 of the Federal Anti-Tampering Act.
Q. If the grapes had been injected by somebody unrelated to the seller who was ultimately the target of your investigation, but the seller knew that they had been injected and still went ahead and shipped the grapes, would that be a violation?
MR. FOX: Objection to the form.
A. Yes, of course.
BY MR. SLATER:
Q. What would that be a violation of?

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A. Well, that could be a violation of the Food, Drug and Cosmetic Act if they knowingly shipped a product that they knew to be contaminated.
Q. If ZHP knowingly sold valsartan and knew that it had NDMA in it, would that be a violation of the -- of any regulations or laws?
MR. FOX: Objection to form. No foundation.
A. That depends.
BY MR. SLATER:
Q. If before FDA dis -- rephrase.
If before ZHP disclosed to the FDA that there was NDMA in its valsartan, if ZHP had been selling the valsartan for a period of time knowing that anyway and it still sold the product, would that have been a violation?
MR. FOX: Objection to form. No foundation.
A. It depends.
BY MR. SLATER:
Q. Depends on what?

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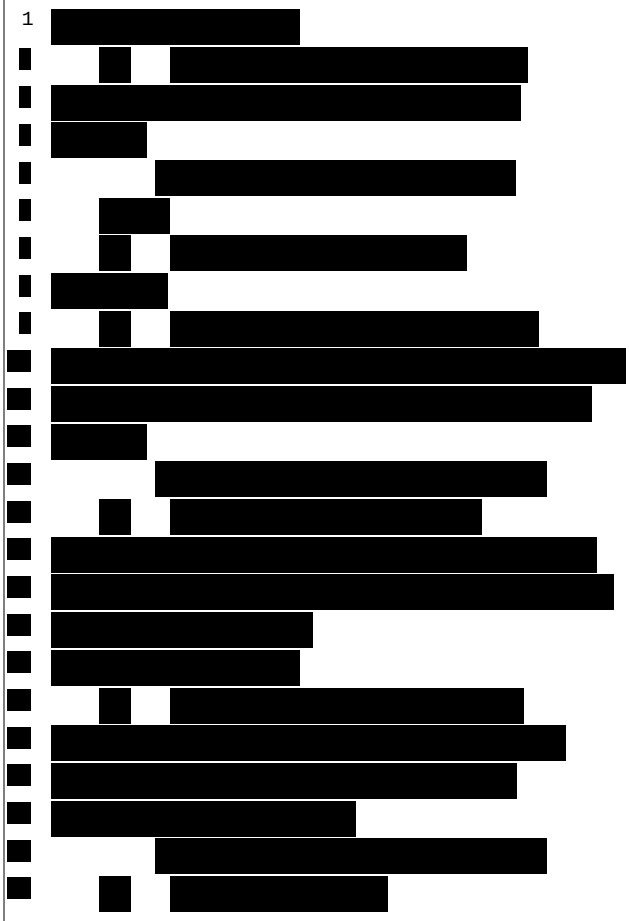
A. Depends on the levels of NDMA, what was known about it, whether they posed a hazard to people who might ingest the product. A variety of factors.
Q. So you're not able to form an opinion based on my question?
A. Not based on your question.
Q. Okay. If we go to page 12 of your report, the last matter listed is October 2021 and continuing, a "Contractual dispute between two pharmaceutical companies over cost recovery from a recall alleged to have been necessitated by GMP deviations at the contractor."
Can you tell me the name of that matter?
MR. FOX: It's subject to a confidentiality order. But, David, you can tell him the name of the matter.
THE WITNESS: Okay.
[redacted]



Q. Good manufacturing practices requires a manufacturer to recognize potential creation of impurities so that they can be assessed, correct?

MR. FOX: Objection to form.

A. If information comes to light that raises that suspicion, GMP would require that it be looked into.

MR. SLATER: Chris, go to Exhibit A of Mr. Chesney's report, please.

Q. Mr. Chesney, Exhibit A to your report is your CV. Is that your up-to-date CV?

A. It is.

Q. Have you ever given any presentations as a consultant -- rephrase.

After you left the FDA, did you ever give any presentations regarding the application of GMP to the manufacture of API or finished dose?

A. Not as the sole subject in the presentation.

Q. But that's something that's come up as part of some presentations?

A. Yes.

Q. Do you have those presentations still?

A. Some.

Q. Have you given any presentations -- rephrase.

Since the time you left the FDA, have you given any presentations regarding what a GMP-compliant risk assessment for a drug manufacturing process, whether API or finished dose, would involve?

MR. FOX: Objection to form.

A. Not as the sole subject of a presentation.

BY MR. SLATER:

Q. But again, something that's come up in the course of some presentations?

A. Yes.

Q. Are those presentations you still have?

A. Some.

Q. When you were at the FDA, did you give any presentations regarding what GMP required in terms of a risk assessment in connection with the manufacturing process for API or finished drug?

A. No.

Q. When you were at the FDA, did you ever write any reports or sign off on any reports addressing whether or not there was a GMP violation in connection with the risk assessment for a manufacturing process for either API or finished drug?

MR. FOX: Objection to form.

A. Not specifically, no.

BY MR. SLATER:

Q. When you say "not specifically," does that mean -- what does that mean?

A. I reviewed and signed off on many reports involving API manufacturing. But in the era when I was working for the

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FDA, the requirements and expectations for documentation of risk assessment were not as detailed or well understood as they are today.

MR. SLATER: Let's go, Chris, if we could, to Exhibit B, please.

Q. And, Mr. Chesney, you're welcome to look at your hard copy report as well as I ask you questions if it's easier, whatever you think -- whatever is easiest for you. Okay?

A. Thank you. I have it open here. I'll try to work off the screen. If I need to stop, I'll let you know.

Q. Fair enough.

Exhibit B is titled "References," and it's my understanding those are the materials that -- well, actually let me rephrase it.

Exhibit B is titled "References," and there's a list of 129 items. Did you read all of those items?

A. I, at minimum, read them cursorily, but I didn't necessarily read

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every word in every item, no.

Q. With regard to the -- let me start over.

The first reference is the Expert Declaration of John Quick. Did you read that?

A. Yes.

Q. Number 2 is the Expert Declaration of Rena Conti. Did you read that?

A. I did.

Q. Did you find that to be relevant to the work you were doing?

MR. FOX: Object to form.

A. Mr. Quick's declaration, yes.

Dr. Conti's was helpful from a contextual standpoint, but I don't believe I relied on it to any great extent.

BY MR. SLATER:

Q. She is an economist. You didn't provide any opinions regarding economics or economic damages, right?

A. No, I did not.

Q. Number 3 is the Plaintiffs'

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Memorandum of Law in Support of their Motion for Class Certification of Consumer Economic Loss Claims. Did you read that?

A. Cursorily.

Q. And I didn't see any opinions in your report regarding whether or not this matter was suitable or not for class certification. Am I correct that's not an issue you addressed?

A. That is not an issue --

MR. FOX: Objection to form.

David, you have to slow up.

THE WITNESS: Sorry.

MR. FOX: Objection to the form.

You can answer.

A. That is not within my area of expertise, and I did not address it, no.

BY MR. SLATER:

Q. And I -- rephrase. The second -- rephrase.

The next reference is reference 4, Memorandum of Law in Support of the Medical Monitoring Plaintiffs' Motion for

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Class Certification. Did you read that?

A. Again, cursorily.

Q. What, if anything, about your cursory reading of those two memorandums of law was of any significance or use to you; anything?

MR. FOX: Objection to the form.

A. It was of use to me in understanding the context and the background, but not the details of fulfilling my remit in this matter.

BY MR. SLATER:

Q. Was there anything you read about in those briefs, those memorandum of laws -- memorandums of law that you said, Well, that's interesting, I should probably look at that, so -- and did you ask the lawyers, Hey, can you get me this document or that document, or this testimony or that testimony that you read about in the briefs? Did that happen at all?

A. I don't recall it happening. It was months ago.

Q. With regard to the materials here, I can assure you we're not going to go through every single one of them because that would take a while, I want to ask you a few general questions about the references here.

Did you ask for any specific materials when you were engaged in this matter where you said, Look, this is what you have to provide me so I can formulate an opinion?

A. I may have asked for one or two items. I was provided with a great volume of material. The first thing I did was try to organize it, sort it out, see what was there.

And then as I got into the details of some of the items, there were things that I wanted to see that had not been provided.

Q. What, if anything, did you ask for that had not been provided to you in the course of your work in this matter?

A. One I recall was that when ZHP initiated the recall of their product, it is FDA's common practice to send what's called a

recall classification letter. It's a template letter that says the agency agrees with the decision, and informs the recalling company of the class FDA has assigned to the recall.

I don't believe that was in the initial package, and I did ask for that document.

Q. Anything else that you requested?

A. I remember that one specifically. There may well have been others. This was a very voluminous document set, and as I went through it, if I found there was something I either could not find or felt I needed, then I would request it.

But I didn't keep a list of what I asked for separately from what was volunteered to me at the outset.

Q. You told me earlier that those facts that you found to be important to you in formulating your opinions were discussed in your report.

So can I trust that to the

extent you read these materials and saw something that you felt to be of significance you related it in your report?

A. Yes.

Q. Item number 5 on the reference list is the Third Party Payors' Brief in Support of Motion to Certify Class. Did you read that?

A. I glanced at it.

Q. Is there anything of significance about that that you can point to now?

A. No.

MR. FOX: Object to the form.

BY MR. SLATER:

Q. Item number 11 is the Prinston Pharmaceuticals Audit Report, dated January 31, 2012, for inspection dates January 31, 2012. Did you read that?

A. Yes.

Q. I don't think I saw it referenced at all in your report in any specificity, is that correct?

A. I suppose. I don't recall

referencing it. And there are several similar reports. I -- at this point by memory I can't distinguish one from the other.

Q. Do you know if you read each of the audit reports or not?

A. I looked at all of the listed reports, yes.

Q. And because they were not discussed in any -- at all in the report, can I assume that you didn't find anything to be of any real significance in those reported reports?

MR. FOX: Objection to form.

A. Not for the purpose I was asked to fulfill.

BY MR. SLATER:

Q. What did you have an understanding -- rephrase.

What was your understanding of your role? What were you asked to opine on?

A. I was asked to opine on what the documents in this matter caused me to think of the GMP compliance status of ZHP

facilities.
Q. Am I correct that your opinions regarding GMP were confined to ZHP and its manufacturing of the API?
A. Yes.
Q. I didn't see any discussion or opinions regarding Prinston, Solco, or Huahai US. Am I correct you gave no opinions regarding their actions or their compliance or noncompliance with GMP?
A. That's correct.
Q. I also saw no discussion of ZHP's manufacturing of the finished dose products. Am I correct that's not an issue you addressed in your report?
MR. FOX: Objection to form.
A. At least one of the FDA inspections touched on that, and I may have summarized some of the findings from that inspection. But I did not focus greatly on the finished dose for manufacturing issues.
BY MR. SLATER:
Q. I didn't see any opinions regarding ZHP's manufacture of finished dose

product. Is that correct, you didn't actually offer any opinions specific to that issue?
A. Not that I can recall.
MR. SLATER: Chris, can you go down to item number 19, please?
Q. Number 19 on this list is ZHP Genotoxicity Statement, dated July 6, 2016, and it has a Torrent Bates number.
Do you see that item?
A. I do.
Q. Is that something you read?
A. If it's on the list I did, yes.
Q. And I can tell you, and you can tell me if this comports with your recollection, that the genotoxicity statement is a representation that there were no genotoxic impurities in the valsartan API being sold by ZHP. Is that your understanding?
MR. FOX: Objection to form.
A. That is my recollection.
BY MR. SLATER:
Q. Did cGMP at that time in July

of 2016 require that such a statement be accurate?
MR. FOX: Objection to form.
A. All GMP statements are required to be accurate.
BY MR. SLATER:
Q. And this would be a GMP statement, correct?
MR. FOX: Objection to form.
A. It's a statement as to the presence or absence or impact if it is present of toxic compounds in the product. It's not really a GMP statement per se.
BY MR. SLATER:
Q. The genotoxicity statement whereby ZHP represented that no genotoxic impurities are present in the substance was certainly required to be a true statement if that's what they were saying, right?
MR. FOX: Objection to form.
A. Yes, any such statement submitted to the FDA would be required to be true, yes.
///

BY MR. SLATER:
Q. What would be the regulatory framework within which such a statement would be evaluated, if it turned out it wasn't true?
MR. FOX: Objection to form.
A. I'm not sure I understand your question.
BY MR. SLATER:
Q. You said that such a statement -- rephrase.
You agree with me that the statement that no genotoxic impurities are present in the substance was required to be true, right?
A. Yes.
Q. If that statement was false, what would be the regulatory or other framework within which that would be evaluated?
MR. FOX: Objection to form.
A. That would depend on the purpose for the submission of the statement.
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BY MR. SLATER:
Q. If the statement was made to allow a downstream purchaser of ZHP's API to be confident that the API did not contain genotoxic impurities, what would be the framework for evaluating that statement?
MR. FOX: Objection to form.
A. First of all, whether or not it was true and accurate. And it would not be a GMP statement per se. If it were submitted to the FDA directly because the agency requested it or in connection with a pending application or something of that sort, then it would come under the regulations for new drug applications or abbreviated new drug applications.
BY MR. SLATER:
Q. Any time that ZHP made a representation to the FDA as to whether or not there were genotoxic impurities in the valsartan API, that would come within the ANDA regulations, is that correct?
MR. FOX: Objection to form.
A. It depends on the context, but

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much of the time, yes.
BY MR. SLATER:
Q. Any statements ZHP made to the FDA about whether or not there were genotoxic impurities in the valsartan API was required to be a true and accurate statement, correct?
A. Yes.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. You told me a few moments ago that your task in this matter was to review the documents provided to you and to evaluate the GMP compliance status of the ZHP manufacturing facility based upon your review of those documents, correct?
A. Yes.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. Did you rely on the attorneys who provided those documents to you to make sure that you had all of the documents relevant to forming such an opinion?
A. Between the initial information they provided and responding to subsequent

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requests that I may have made, yes.
Q. You would agree with me that if there were material documents, meaning material -- rephrase.
You would agree with me that to the extent there were documents that would be material to your formation of that opinion that were not provided to you, that could potentially be problematic, correct?
MR. FOX: Objection to form.
Calls for speculation.
A. I'm not aware that there were any such documents. And if I felt something was needed and I didn't have it, I requested it.
BY MR. SLATER:
Q. You told me about the one document you requested regarding the recall. Is there any other document you can recall that you asked for?
MR. FOX: Objection. Asked and answered.
A. I did a little independent research as well, looking at publicly

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available data on the FDA's website regarding the compliance history of ZHP. That was not supplied by the attorneys.
BY MR. SLATER:
Q. Ultimately your opinion is dependent on the materials you reviewed, correct?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. If I were to be able to show you documents during the course of this deposition where you would say, You know, that's a document that would have been material to me so I would have to look at that document and reevaluate my opinion, that would -- if that were to happen, that would place your opinion in question until you'd have the chance to review that document and determine whether it affected your opinion, right?
MR. FOX: Objection. Calls for speculation.
A. I have no way of knowing that

without seeing the specifics.
BY MR. SLATER:
Q. Let me talk to you -- and let me be specific in what I'm asking you.
In terms of your approach to this case, your methodology, you've already told me that you relied on the documents that you reviewed to form your opinion. We've already gone over that.
What I'm getting at is, if I were to show you a document or ask you about a type of document and you said, Well, I didn't see that, and if that existed that would be important to me, something I would have needed to take into account in order to form my opinion in this case, if that were to happen, would you agree with me that you would then want to review that document and then offer an opinion based on everything you had seen inclusive of that document?
MR. FOX: Objection to form.
A. It would depend on the specifics.
///

BY MR. SLATER:
Q. One of the things that you talked about in your report were internal standard operating procedures which you mention can go by various nomenclatures; standard operating procedures, standard management procedures, they can have various titles, but you talked about that concept in your report, right?
A. Yes.
Q. And I think -- you can correct me if I'm wrong, I think what you said was those internal -- and I'm going to call them generically standard operating procedures or SOPs, okay?
A. That's fine.
Q. I think you said in your report that to the extent a company actually adopts such SOPs as part of their GMP processes, they're required to comply with those SOPs.
Did I understand that correctly?
A. Yes.
Q. So if ZHP had internal SOPs

relevant to the issues that you looked at, you would have expected to be provided those so you could take those into account in forming your opinion, correct?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. So for example, with regard to -- well, withdraw that.
If, in fact, there were internal SOPs from ZHP that you were not provided that relate, for example, to the change control process or the change control that was -- rephrase.
If there was a -- rephrase.
If there was an internal standard operating procedure from ZHP addressing the change in manufacturing process, you would have wanted to see that, right?
MR. FOX: Objection to form.
A. I did see one related to that.
BY MR. SLATER:
Q. Is it listed on your list of

references?
A. No.
Q. Is it listed in your report in a footnote?
A. Yes.
Q. Is that 18.01?
A. That's a typographical error. I've discovered it should be 18.08.
The reason it may not be listed in the references is it was an attachment to the warning letter response that ZHP sent in, so it was included in another item that is referenced.
Q. Why are you saying that 18.08 should have been listed as opposed to 18.01?
A. Because I looked at it over the weekend and double-checked it against the footnote in my report, and found the report has a typo in that number.
Q. So the S -- it's actually an SMP.
A. Yes.
Q. Okay. So the SMP that you saw was 18.08?

A. Yes.
Q. You did not see any of the other iterations of SMP 18, correct?
A. I did not, but the .08 version has a complete revision history, so I was able to tell from that what changes had been made over time.
Q. As you sit here now, do you know what the form of that SMP was when the manufacturing change process was being evaluated by ZHP?
MR. FOX: Objection to form.
A. I'm sorry, you said the form? I don't follow your question.
BY MR. SLATER:
Q. Let me ask you this. Did you ask to be shown the SMP that was actually in effect when ZHP was going through the change control process?
A. By retrospectively looking at the revision history, I believe it was version 5 or version 6, I don't recall as I sit here. But I was able to see what changes had been made since then in '08, and use that

to determine what would have been there in that earlier iteration.
Q. Did you discuss that at all in your report?
A. No.
Q. Is this just an issue that you became aware of this weekend, as you said?
A. Oh, just the incorrect citation of the number I became aware of, yes.
Q. The wording of the SMP that governed the change control for the manufacturing process is an important document in this case, correct?
MR. FOX: Objection to form.
A. It's an important document, yes.
BY MR. SLATER:
Q. And the version that would be most significant would be the version that was in effect in 2011 when the manufacturing process change was being evaluated at ZHP, correct?
MR. FOX: Objection to form.
A. Yes, that would be important.

Whether it would be most important or not is -- I'm not prepared to say, but it certainly would be important.
BY MR. SLATER:
Q. Well, in terms of whether or not ZHP complied with the SMP governing change control, the version that was in effect when ZHP conducted that change control review would be the one that you would want to look to to determine whether or not it was complied with, right?
MR. FOX: Objection to form.
A. I was able to use the revision history to see what changes had been made since that time, and as I sit here now, I can't explain that in detail because I don't have the document in front of me. But I concluded I had enough information there to establish that they did have a procedure for that.
BY MR. SLATER:
Q. Is the answer to my question yes, that the version that was in effect when the change was being evaluated, that would be

the one that would be most significant because that would have been the one in effect at the time?
MR. FOX: Objection to form.
A. That would have been the one in effect at the time, and that would be the one that GMP would require them to follow, yes.
BY MR. SLATER:
Q. And you testified that you believed that version 5 or 6 would be the one that was in effect at the time of the change, and that's the one that would be most significant, that's your understanding?
MR. FOX: Objection to form.
A. I can't be positive without looking at the version history in the actual attachment that's referenced here, but from memory, I think it was in that vicinity. It was either 5 or 6. I'd have to look again to be sure.
BY MR. SLATER:
Q. If ZHP failed to comply with the SMP 18 version that was in effect when it did its change control review, then it

violated GMP, correct?
MR. FOX: Objection. Form.
A. That would be a deviation from GMP, yes.
BY MR. SLATER:
Q. I'm not going to pull them out right now, but there were also some ICH documents that you referenced in your report as well, correct?
A. Yes.
Q. For example, ICH Q7A and Q7, that's the good manufacturing practice guidance for active pharmaceutical ingredients, that's an important document in this case, right?
MR. FOX: Objection to form.
A. The correct nomenclature is Q7. They dropped the A off of it a few years ago.
BY MR. SLATER:
Q. In the 2001 version it said Q7A, and then in 2016 they dropped the A.
Does that sound right?
A. Yes.
Q. So for our discussion today, we

can just call it the Q7?
A. Yes.
Q. Was ZHP required to comply with Q7 at the time that it was evaluating the change in the manufacturing process as a matter of GMP?
MR. FOX: Objection to form.
A. In the US regulatory hierarchy, Q7 stands as nonbinding guidance, not as a regulation.
BY MR. SLATER:
Q. Well, if it's a nonbinding guidance, why does anybody look at it if it has no impact on anything that anyone is actually going to have to do?
A. Because there is no binding regulation for GMP for API, only a broad statutory requirement.
Q. In terms of how the broad statutory requirement to comply with GMP is interpreted, Q7 is actually a significant source, correct?
A. Yes.
MR. FOX: Objection to form.

BY MR. SLATER:
Q. And in your industry, it's accepted that a violation -- rephrase.
And in your industry, it's accepted that a failure to comply with Q7 would amount to a GMP violation, correct?
MR. FOX: Objection to form.
A. Not exactly.
BY MR. SLATER:
Q. Are there circumstances where the failure to comply with Q7 constitutes a violation of GMP?
A. Are there circumstances -- pardon me. Say again? Are there circumstances when it does?
Q. Yes.
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. I'm saying in and of itself where somebody would say, Well, because you didn't comply with this aspect of Q7, that constitutes a violation of GMP.
MR. FOX: Objection to form.

Incomplete hypothetical.
A. That involves the application of judgment. It is not a linear correlation. If you deviate from a guideline, you're expected to have a justified reason why what you are doing to comply is as good as or better than what the guideline prescribes.
So there may be times you don't meet the guideline literally, but what you're doing is perfectly adequate.
BY MR. SLATER:
Q. I think what you're saying is if you're going to deviate from the Q7 guideline, you need to be able to explain why the alternative approach you took was acceptable?
A. That's correct.
Q. And acceptable would mean that it -- well, let me rephrase.
And acceptable would mean that your own process or your own approach accomplished the same thing that Q7 sought to approach, correct?
MR. FOX: Objection to form.

A. Yes.
BY MR. SLATER:
Q. So, for example, if the issue was a -- the Q7 requirement that a thorough scientifically based risk assessment be performed in order to identify potential genotoxic impurities that may result from a change in manufacturing process, if ZHP failed to actually identify that potential impurity, ZHP would need to show why its approach either -- it would need to show why its approach which deviated from Q7 -- let me rephrase, because I think that I actually answered my own question.
MR. FOX: I'm going to object to it anyway, Adam.
MR. SLATER: I took it back. You can't object to the take-back.
BY MR. SLATER:
Q. If ZHP did not apply Q7 to its risk assessment for the manufacturing change to the zinc chloride process, ZHP would need to justify why it took an alternative approach, correct?

MR. FOX: Objection to form.
A. Mr. Slater, your question assumes that that level of detail is in Q7, which it is not. If memory serves, Section 2.22 of Q7, line item 4 is one sentence that simply says that when deviations occur they must be investigated. It doesn't mention genotoxic impurities or anywhere near the level of specificity that was embodied in your question.
BY MR. SLATER:
Q. Can we agree when ZHP performed its risk assessment in connection with the manufacturing process change to the zinc chloride process that ZHP was required to apply current scientific knowledge?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. You said something earlier about from what you saw there was a process that ZHP had, and that's part of GMP, is that you have to have a process to follow, right?
A. Yes.

Q. GMP also requires that the process be followed thoroughly and correctly, right?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. So going through the motions and saying, Well, we checked the boxes and we technically did a risk assessment, that's not enough; you have to actually actively perform the risk assessment and apply the available scientific knowledge in evaluating that process, right?
MR. FOX: Objection to form.
A. I don't -- I fail to understand the difference between saying you did a risk assessment and doing a risk assessment, which is what your question implied to me, sir.
BY MR. SLATER:
Q. Well, what I'm saying is, is it enough to just go through the motions and not apply the scientific knowledge that's available and just check the boxes and then you're okay?

MR. FOX: Objection to form.
A. I fail to understand the thrust of your question. I really don't follow you.
BY MR. SLATER:
Q. Okay. I understand that you have told us you don't have the scientific expertise to determine whether or not -- well, rephrase. Let me ask you this, if I'm right.
Am I correct that you have told us in your report you do not have the scientific expertise to evaluate whether or not ZHP adequately took into account the scientific knowledge at the time of the manufacturing process change such that you can't offer an opinion as to whether or not ZHP met or did not meet current good manufacturing practices?
MR. FOX: Objection to form.
A. I am not a subject matter expert in process chemistry or pharmaceutical chemistry, nor was I when I was at the FDA.
The way things were done there and the way I do them in my consulting

practice is in a multidisciplinary collaborative sense where I call on the knowledge and expertise of other subject matter experts to assist in areas where I don't feel I have all the knowledge and experience necessary.

That's the way these things are worked out both in the agency and in the consulting work that I do.

BY MR. SLATER:

Q. In response to my question, "am I correct," is the answer yes?

MR. FOX: Objection to form.

A. I don't -- I am not a subject matter expert in process chemistry or pharmaceutical chemistry, so there are limitations for how far I could take that analysis, yes.

BY MR. SLATER:

Q. And am I correct that because you do not offer any opinions regarding the scientific adequacy of the risk assessment, you're not offering an opinion at this time as to whether or not ZHP met its GMP

obligations?

MR. FOX: Objection to the form. Misstates testimony.

BY MR. SLATER:

Q. Am I correct?

A. In my report I indicate those areas where I must defer to appropriate -- people with appropriate scientific expertise.

Q. And that's one of those areas, right?

MR. FOX: Objection to form.

A. It may be. As I recall it is, but I'm not looking at that part of the report at the moment.

BY MR. SLATER:

Q. Well, I'm asking you as you sit here right now, am I correct that because you're not able to offer an opinion as to whether or not ZHP's risk assessment was adequate from a scientific perspective, you're not in a position to offer an opinion as to whether ZHP's risk assessment was adequate from a GMP perspective --

MR. FOX: Objection to the

form.

Sorry, Adam.

BY MR. SLATER:

Q. -- am I correct that you cannot do so because of your lack of scientific expertise?

MR. FOX: Objection to the form. Misstates testimony, no foundation.

A. I would require the assistance of scientific subject matter experts to have a fully formed opinion of that, that's correct.

BY MR. SLATER:

Q. Well, when you say to have a fully formed opinion, I just want to make sure before we get off this point that we're both clear.

You don't have an opinion as you sit here right now as to whether ZHP satisfied good manufacturing practices when it made the manufacturing process change because you're not able to evaluate the scientific adequacy of that risk assessment,

is that correct?

MR. FOX: Objection to form.

A. I'm not able to determine independently whether it was feasible for them to have brought the scientific principles to bear beyond what they did, because I am not a pharmaceutical chemist or a process scientist, and not aware of what the state of the art may have been at that point in time. That's what I would need help on. I can't evaluate other aspects of the risk assessment.

And assuming the science is sound, I can then offer an opinion that if that is true, then the effort complies with GMP. But it's subject to validation by appropriate scientific expertise.

BY MR. SLATER:

Q. At this point you don't have an opinion as to whether ZHP met or did not meet GMP because you do not at this time have a basis to evaluate the scientific adequacy of the risk assessment. Is that a correct statement?

MR. FOX: Objection to form. Misstates testimony and his report.

A. Assuming the science is supportable I can form an opinion, but I would need additional input in order to be confident.

BY MR. SLATER:

Q. I understand what you could do if certain information were provided at a later date.

But as you sit here now, you're not able to form that opinion because you don't have that information one way or the other, correct?

A. That's correct.

MR. FOX: Objection to form.

BY MR. SLATER:

Q. I'm sorry, over the objection you said "that's correct," right?

A. Yes.

Q. You said that -- I think you used words to the effect of -- rephrase.

When you were talking a few moments ago you referred to the feasibility

of having certain scientific knowledge, or something to that effect. I know I'm not directly quoting you. But I think you said something to that effect.

Did I hear you right?

A. Yes.

MR. FOX: Objection to form.

BY MR. SLATER:

Q. If it was feasible for ZHP to be aware of the scientific processes that led to the creation of the NDMA impurity at the time it did its risk assessment, then it violated GMP by failing to identify that potential impurity, correct?

MR. FOX: Objection to the form. Misstates testimony, no foundation.

A. If it was feasible for them to apply appropriate science at that point in time and they failed to do so, it would raise certain questions and would require further study on my part and collaboration with the appropriate scientific experts so that I could fully understand the details before I

would be able to reach a conclusion I would be confident in. It would require study and discussion.

BY MR. SLATER:

Q. Well, I would like you to assume that it was feasible for ZHP to know at the time that it was performing its risk assessment on the zinc chloride process that under those manufacturing conditions DMF could degrade and create dimethylamine, and that it was also feasible to know that under those manufacturing conditions that dimethylamine could react with the nitrous acid that resulted from the sodium nitrate at the quenching stage, and that that reaction could form NDMA or other nitrosamines, I'd like you to assume that that was feasible for them to know at the time, and they did not -- as we know, they did not identify that potential impurity and that potential reaction, we know that.

So if my hypothetical is correct, ZHP violated GMP in its risk assessment, correct?

MR. SLATER: Objection to form. Incomplete hypothetical.

A. Part of a proper vetting of that position would require understanding whether analytical methodology existed that could detect NDMA at whatever level it might or might not be present, and how much reliability could be placed in that analytical methodology.

So that's another example of the sort of thing I would need the help of pharmaceutical chemistry expertise to better understand.

BY MR. SLATER:

Q. The analytical methodology would be GC-MS, gas chromatography-mass spectrometry, right?

MR. FOX: Objection to form.

A. That's one of, I believe, three methods that are out there now that were not at the time in question.

BY MR. SLATER:

Q. I'd like to expand my hypothetical to address the comment you just

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made, and I'd like you to assume that it was feasible based on technology available in 2011 for ZHP to have identified the NDMA if they were looking for it as a potential impurity. I'd like you to assume that technology was available.

Having expanded my hypothetical accordingly, you would agree that under those circumstances ZHP would have violated GMP in its risk assessment, correct?

MR. FOX: Objection to form.

A. Well, you're asking me to make a lot of assumptions, which I do not know whether they're true or not, and I frankly struggle with that. I'm not sure I can agree to that hypothetical.

BY MR. SLATER:

Q. We'll come back to it.

You said you normally work with a multidisciplinary team to form your GMP opinions in this type of a context?

A. I said that I did that when I was at the FDA, and that in consulting I still do that to this day.

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Q. That did not occur here, right?

A. It did not, because my retention was under a particular agreement, and I didn't have the benefit of being able to call upon colleagues and share details with them due to confidentiality.

Q. You did not rely on the opinions of any subject matter experts regarding the scientific questions here in forming your opinions. That has not occurred, right?

MR. FOX: Objection to the form. Misstates his report and references.

BY MR. SLATER:

Q. I'm correct, right?

A. I took what was available from the FDA communications and the record that I had in front of me and based my opinion on that.

Q. I didn't see any discussion in your report of you relying on any particular subject matter experts regarding the science to form your opinions. That's not something

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you did in your report, right?

A. That's right.

MR. FOX: Objection to form. Misstates testimony.

A. What I did was I mentioned specifically in the report the areas where I was unable to carry my opinion beyond the point it's at because I would need to defer to others with appropriate scientific expertise. Those areas are highlighted.

BY MR. SLATER:

Q. I want to come back now to my hypothetical. And it's no secret I'm asking you these questions as a hypothetical because I think I can prove every single aspect of it very easily. So this is not some -- I'm just telling you this is no farfetched hypothetical. So let me -- having said that, let me rephrase.

Were you provided the report of Dr. Steven Hecht?

A. No.

Q. Do you know who he is?

A. No.

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Q. Were you -- rephrase.

Were you provided, other than Mr. Quick's declaration and Ms. Conti's declaration, any other plaintiff expert reports or declarations?

A. No.

Q. I'm going to try this one more time, but I'm going to try to do it more coherently.

Let me ask you this before I go on. Actually let me do this, actually, the way that I want to.

All right. I'm going to try to ask you the hypothetical in a little more condensed fashion now also addressing the analytical methodology issue that you questioned me on so I can put it all together in one question, and then we'll see if, maybe by me doing that, if you'll be able to answer that question, okay?

A. Sure.

Q. I'd like you to assume that at the time -- rephrase.

I would like you to assume that

at the time ZHP was performing its risk assessment on the zinc chloride manufacturing process that it was scientifically feasible for ZHP to know that, under the manufacturing process conditions that were proposed, that the DMF that they had added to the process could degrade, and that one of the degradings from that could be dimethylamine, and that under the proposed manufacturing conditions that dimethylamine could react with the nitrous acid that would be present during the quenching phase due to the presence of sodium nitrate, and that that reaction could yield NDMA.

I'd like you also to assume that at the time it would have been scientifically feasible to apply testing to see if there was NDMA there if one were looking for it. I'd like you to assume those facts.

If those facts are true, you would agree with me that ZHP's failure to take into consideration what I just asked you about would have violated current good

manufacturing practices at the time?

MR. FOX: Objection to the form. Incomplete hypothetical, calls for speculation.

A. If I understand your question correctly, Mr. Slater, if all those things were feasible and were known to ZHP, they should have taken them into consideration.

BY MR. SLATER:

Q. We know they did not, because you've seen their documentation, so we know ZHP never took into account the potential chemical reactions I went through with you, correct?

MR. FOX: Objection to form.

A. I can't reach that conclusion. ZHP submitted a tremendous amount of very detailed scientific analysis, a lot of structural chemistry diagrams and other things, and this is where my expertise drops off, and I would need others to look at that and determine whether they, in fact, understood the principles you've just outlined or not. I cannot reach that

conclusion by reviewing the information they submitted.

BY MR. SLATER:

Q. If ZHP did not take into account the chemical reactions that I just described to you in my hypothetical, then they violated good manufacturing practices, correct?

MR. FOX: Objection to the form. Misstates testimony, calls for speculation.

A. What I -- I'm sorry? I heard an echo there, I guess. I thought someone was asking another question.

BY MR. SLATER:

Q. No, no one said anything. But let me just be clear on my question before you answer.

I'm going back to my original question, which is, assuming the accuracy of that hypothetical, assuming that it was scientifically feasible for ZHP to know those things, and assuming they did not take them into account, they violated good

manufacturing practices in that risk assessment, correct?

MR. FOX: Objection to form. No foundation, misstates testimony, and calls for speculation.

A. The GMP requirement is very high level, it's for a thorough investigation. Nowhere does it specify what the elements of a thorough investigation are; it leaves that up to judgment.

And certainly if there is material information that was either not considered, omitted, whatever, then that risk assessment would be less than it should be based upon those facts.

BY MR. SLATER:

Q. When you say "less than it should be," that would mean not compliant with GMP, correct?

MR. FOX: Objection to form.

A. That calls for a conclusion that I'm not prepared to reach. It would be less than I would hope to see certainly.

But it's difficult sometimes to

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discern when you're talking about something would simply improve an otherwise compliant practice or make the difference between compliance and noncompliance.
BY MR. SLATER:
Q. Are you aware that there was -- well, let's jump forward a little bit, actually, since we're cruising along here. Just find a paperclip. We'll come back to this a little bit.
Let me ask you this: On your Exhibit B, did you actually review the change request form which laid out the evaluation that ZHP did of its change in manufacturing process to the zinc chloride process? Because I didn't see that referenced on your reliance list -- reference list, I should say.
A. I think it was incorporated in another document that is on that list, but it would take me some time to check back and find it. I do recall seeing that form, but I don't remember much about it as I sit here.
Q. I didn't see the change request

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form referenced anywhere in your report. Did I miss that, or am I correct that it's not referenced?
MR. FOX: Objection. Asked and answered.
A. It may not have been referenced by that name. I think it was a part of another document set that I reviewed and relied upon. And if memory serves, I believe it was the response to the warning letter, but I would have to go back and check through these references to determine that for certain.
BY MR. SLATER:
Q. The documentation of the risk assessment for the change in manufacturing process, that documentation would have been very important to you in forming your opinion here, correct?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. Yet there's no place in your report where you actually discuss that

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document at all, correct?
A. What do you mean by "that document"? Which document are you referring to?
[redacted]
anywhere in your report or discussed at all in your report. Am I correct?
A. I don't recall specifically citing it. I do recall seeing it.
Q. The change request form documenting what was done and what was considered would be a critical document to you in forming an opinion as to whether or not ZHP met its GMP obligations, right?
MR. FOX: Objection to form. Argumentative, and misstates prior testimony. Asked and answered.
A. Subject to input regarding the rigor of the science, yes.
MR. SLATER: Counsel, you keep saying that I'm misstating testimony.

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I don't understand why you keep saying that. I'm not stating his testimony.
I mean, I think we have to at some point -- I would ask you politely if we can just limit the objections to legitimate objections, please.
MR. FOX: It was a legitimate objection, Adam. You previously asked him whether it was important, now you're asking him whether it's critical. You were changing the question on him, and you had already asked about that.
BY MR. SLATER:
[redacted]

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[redacted]

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Q. As a matter of ICH guidance, if something is deemed a critical change, it requires a higher degree of scientific rigor in performing the risk assessment, right?

MR. FOX: Objection to form.

A. Generally speaking, yes.

BY MR. SLATER:

Q. Do you know whether or not -- well, rephrase.

You said you think that you saw the change request form as an attachment to another document. Did you ever ask counsel, Is this the complete change request form with all attachments?

A. I don't recall ever asking that question, no.

Q. Do you have any knowledge as to whether or not the change request form that you think you saw attached to another document was the complete change request form with all attachments? As you sit here now, do you have any idea?

A. I do not as I sit here now.

Q. And without seeing the complete

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document and comparing it to what you did have, you don't know whether there's material information that you didn't have available to you, right, by definition?

A. I'm not sure I understand your question, sir.

Q. Well, you don't know what you don't know, and since you don't know if you saw the complete document you don't know if you were missing material information from the change request form and its attachments, right?

MR. FOX: Objection to form.

A. If there was material information that was not made available to me, I'm not aware of that, and yes, it would be of concern.

BY MR. SLATER:

[redacted]

A. I don't recall.

Q. Would that be an important

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consideration in forming an opinion as to whether ZHP complied with GMP?

MR. FOX: Objection to form.

A. That's another example of something that I would ask for help from a pharmaceutical chemistry expert to evaluate, but yes, the outcome of that discussion would be important.

BY MR. SLATER:

Q. Were you curious when you were writing your report as to what impurities ZHP considered -- let me rephrase.

When you were writing your report, were you curious as to what potential impurities ZHP considered as part of its risk assessment for the zinc chloride process? Were you curious as to what they looked at?

A. I'm not sure I understand what you mean by was I curious. I reviewed the record, I saw what they did consider, I saw how they documented it, I stated, I think fairly clearly, where my limitations were in my ability to evaluate the science.

Was I curious as to whether

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they looked for certain other things that they might have had no reason to believe were there? No. GMP does not require that you look for things you have no basis to believe are present.

[redacted]

BY MR. SLATER:

Q. As you sit here now, did you say anything about that in your report?

A. Again, I'd have to go through the report to be certain.

[redacted]

Are you saying it might be in the report and you'd need to check your report to see if that's in there?

A. I don't recall that it's there,

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but I wouldn't be prepared to say that definitively without going through the report.

Q. And as you sit here now, are you able to tell me one way or another whether or not -- well, let me ask you this.

As you sit here now, do you have an assumption as to whether or not ZHP considered the potential formation of NDMA or any other nitrosamines as part of the zinc chloride manufacturing process when it performed its risk assessment? Do you have an assumption one way or the other as to whether that was considered?

A. My assumption would be that they did, absent information to the contrary. But I don't recall what those documents said without going back and looking at them again. This was an incredibly voluminous data set, and I don't carry it all around in my head.

Q. What's the basis for that assumption that they did consider the potential formation of NDMA or other nitrosamines as part of the risk assessment?

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A. It's the impression I got of the thoroughness and completeness of the documents that I reviewed from ZHP, the interactions between them and the FDA staff, the FDA questions that came back to them, the entire dialogue that took place there.

Ultimately they did, of course, find those residues in certain batches, and they did the responsible thing and conducted a recall, so at some point in time they did make that identification. I believe that was in 2018.

Q. When you say "they did the responsible thing," do you mean telling their customers and the FDA that there was NDMA in the valsartan?

A. Once they knew that, yes.

Q. When you say that's the responsible thing, it's not only the responsible thing, it was the legally required thing to do, right?

A. Yes.

MR. FOX: Objection to form.

///

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BY MR. SLATER:

Q. As soon as ZHP knew that there was NDMA in its valsartan, it was legally obligated to inform all of its customers and the FDA, correct?

MR. FOX: Objection to form. Calls for a legal conclusion.

A. The regulatory requirement is for them to report that to the FDA in the form of a report called a field alert report.

BY MR. SLATER:

Q. And it's your testimony based on the materials you saw that you understand that ZHP complied with that field alert report regulation in June of 2018?

A. They notified the FDA.

Q. It's your understanding that ZHP notified its customers and the FDA immediately upon learning that there was NDMA in its valsartan? Is that your understanding from what you reviewed?

MR. FOX: Objection to form.

A. The word "immediately" is one I have difficulty with. They did it very soon

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thereafter. I don't know what you mean by "immediate," but it was in very close proximity time-wise to that, yes.
BY MR. SLATER:
Q. The field alert report regulation provides three business days to provide that information to the FDA, right?
A. Yes.
Q. Is it your understanding that ZHP reported that there was NDMA in its valsartan within three days -- business days of learning of that?
MR. FOX: Objection to form.
A. The difficulty with that is it's very difficult to determine in many cases when the clock starts.
I believe they did the responsible thing by reporting it. Once they had certainty as to that information they told the FDA about it, and they did conduct a recall on a voluntary basis.
BY MR. SLATER:
Q. Was the notification of the presence of NDMA in the valsartan to

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customers and the FDA required by good manufacturing practices?
A. No.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. Did good manufacturing practices require that -- well, rephrase. I'll get back to it.
Coming back to what ZHP did as part of its risk assessment -- well, rephrase.
I was asking you before about whether ZHP considered the potential formation of nitrosamine impurities including NDMA, and you said your assumption was that they did consider that, right?
MR. FOX: Can you repeat that, Adam? I missed that.
MR. SLATER: Sure.
BY MR. SLATER:
Q. You told me a moment ago that you assumed that ZHP did as part of its risk assessment take into account the potential formation of nitrosamines as part of the zinc

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chloride process during its risk assessment. You told me that you assumed they took that into account, right?
A. It would appear that they did from the depth of the scientific information they submitted. But again, that's one of those areas where I would turn to the subject matter expertise -- or a person with appropriate subject matter expertise to help me understand how far they carried things and whether that was sufficient to achieve those ends. I didn't --
Q. Go ahead, I'm sorry.
A. I was going to say I made no attempt to evaluate the science independently.
Q. Whether or not ZHP considered the potential formation of nitrosamines as part of the zinc chloride process is an important fact you would want to know, right?
MR. FOX: Objection to form.
A. Along with whether or not it was even reasonable for them to consider that at that point in time. I think that's the

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other aspect of this. There's nothing in GMP that requires you to look for things you would have no basis to believe were there. And that's why the state of the art of the science at that moment in time is important for me to understand in tandem with the other information.
BY MR. SLATER:
Q. Well, my first question is this. One important fact for you to consider in this matter would be whether or not ZHP considered the potential formation of nitrosamine impurities as part of the proposed zinc chloride process when it performed its risk assessment.
Would you agree with that statement?
A. It would be helpful to understand that, yes.
Q. Did you ask the lawyers who retained you if there's any information available to answer that question one way or another?
A. I don't recall asking that

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question.
Q. That's my question. I want to know if you asked them for that. Okay.
A. No.
[redacted]

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[redacted]
MR. FOX: Is this a good time for a break, Adam?
MR. SLATER: I need a couple more minutes. I'd like to continue. I don't want to just arbitrarily take a break now.
BY MR. SLATER:
Q. If there was deposition testimony from corporate representatives of ZHP that definitively answered that question,

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would you like to have been provided that deposition testimony?
A. Yes.
Q. If such testimony exists one way or another, you would actually expect that that would have been provided to you so that you could perform your function here, right?
A. It would have been helpful.
Q. Can you think of any legitimate reason why the lawyers who hired you would not have provided you that deposition testimony if, in fact, it exists?
MR. FOX: Objection. Argumentative.
A. I don't know what the basis was for the document set that I was provided. I can't speculate about what might have been in their minds as to what I would need or what I wouldn't.
BY MR. SLATER:
Q. If there was a feasible scientific basis for ZHP to know that nitrosamines could potentially be formed by

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the zinc chloride manufacturing process that was being proposed, if that was feasible to know, and if the technology existed for ZHP to feasibly test to see if a nitrosamine was being created by this new manufacturing process, then ZHP would have been required to carry out such testing to see if nitrosamines were being created as part of its risk assessment, correct?
MR. FOX: Objection to form.
A. That would have been the right thing for them to do. The requirements don't speak to that level of detail, but that would have been a reasonable thing for them to do, yes.
BY MR. SLATER:
[redacted]

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[redacted]
BY MR. SLATER:
Q. But you, as somebody who holds themself out as an expert on GMP, would look at what the company actually put in force in its own internal SOPs to address its own business, and based on what you've seen you would agree GMP as applied by ZHP would have required that to be done, right?
MR. FOX: Objection to form.
A. If their procedure called for identification or quantitation of known potential impurity risk and they failed to do so, then yes, that would be a failure to follow their own procedure, which by extension is a failure to follow GMP.
BY MR. SLATER:
Q. And you would certainly expect that ZHP or any similar manufacturer would have an internal SOP that would require it to

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identify new impurity risks if they were going to change a manufacturing process, right?
A. That's something they should be considering, yes.
Q. That would be required by GMP under those circumstances, right?
MR. FOX: Objection to form.
A. Broadly, yes, but not specifically.
BY MR. SLATER:
Q. Well, if you were brought in by ZHP or a similar company and asked, We're changing our manufacturing process for this API, would GMP require that that evaluation that we're going to perform evaluate whether any new impurities are being formed, you would say yes, right?
A. Yes.
Q. If you want to take a break -- I'm happy to keep going, Mr. Chesney, your counsel asked if we need a break, I don't need one. I'm happy to keep going because I'm hoping to get done in the afternoon, but

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it's completely up to you. If you want to keep going, I'll keep going.
MR. FOX: We've been --
THE WITNESS: Go ahead, Tom.
MR. FOX: What did you say, David?
THE WITNESS: I was just going to say I could use about ten minutes at this point.
MR. SLATER: All right. Let's take ten minutes.
THE VIDEOGRAPHER: The time is 11:25 a.m. We are off the record.
(Whereupon, a recess was taken.)
THE VIDEOGRAPHER: The time is 11:36 a.m. We are back on the record.
BY MR. SLATER:
Q. I want to talk a little bit about the significance of the risk assessment for a couple minutes with you.
The risk assessment performed -- rephrase.
The risk assessment that was

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required to be performed by ZHP has significance for process validation in the sense that you have to identify potential impurities so that you know to test for them.
Is that a true statement?
A. Generally speaking, yes.
Q. So identification of the potential impurities from a new manufacturing process is really a very important threshold step pursuant to GMP, correct?
MR. FOX: Objection to form.
A. To the extent that it's feasible to do so and you know what to expect, yes.
BY MR. SLATER:
Q. When you say you know what to expect, meaning you know that this is a potential impurity so you know that you need to test for it?
A. Yes. You don't need to conjure up things that there's no rational basis to believe what happened.
Q. And this risk assessment is not supposed to be based on guesswork, it's

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supposed to be based on scientific analysis, right?
A. Yes.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. For example, in a situation like this, a company like ZHP would be expected by GMP to have process chemists evaluating the proposed chemical reactions, and to bring their scientific knowledge to bear to identify the potential impurities that could result, right?
A. Yes.
Q. And they would -- rephrase.
And these process chemists would be expected to not only bring to bear their own knowledge that's in their mind, but also to, to the extent they don't know the answer, to research available medical literature, right?
Let me rephrase because I went all over the place. I meant to say scientific.
And those process chemists

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would be expected to not only employ their own personal knowledge, but also to research scientific literature as well to the extent that it existed, right?
MR. FOX: Objection to form.
A. Any literature reports they're aware of, they should be taken into consideration if they're relevant.
BY MR. SLATER:
Q. And this should be an active process of research and evaluation, right? They should be actively looking to make sure that they turn over the stones that can be turned so they don't miss something, right?
MR. FOX: Objection to form.
A. Well, yes. Within reasonable limits. You don't have to stay in search mode forever. There comes a point in time when you've consulted appropriate reference materials and feel that you have enough to go on. That's a matter of judgment.
BY MR. SLATER:
Q. One of the other important reasons why potential impurities need to be

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identified during the risk assessment is so that not only the process validation can be thorough, but also so that ultimately the specifications for what needs to be tested and what the levels that should be tested for so that those can be set as well, right?
A. Yes.
Q. And I guess the specifications is sort of the other side of the coin from the process validation. Is that a fair assumption? The process validation is when -- it actually doesn't make sense. You don't have to answer that. You roll your eyes, I know I move on.
If there was a GMP violation in the risk assessment, as I have proposed to you through my hypothetical, and ultimately ZHP should have but failed to evaluate the potential nitrosamine impurities that could have resulted from the zinc chloride process, if that's so, and then they went ahead and used that manufacturing process, that process would not be cGMP compliant based on the GMP violation in the risk assessment, correct?

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MR. FOX: Objection to form.
A. That would require me to accept a lot of the assumptions that you're building into your hypothesis.
BY MR. SLATER:
Q. I'm asking you to accept those assumptions.
If those assumptions are -- if the answer is yes, if you accept them, am I correct that the manufacturing process itself would not be GMP compliant?
MR. FOX: Objection to form. Incomplete hypothetical.
A. Well, that's not the way I would put it, Mr. Slater, that the GMP -- or that the manufacturing process would not be GMP compliant. I would simply say there was material information about the risks inherent in that process that had not been identified.
The point in time when this took place, if I remember correctly, was 2011, 2012, something like that. Again, without referring to the references, I can't be sure. But I think the FDA in their public

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statements later on indicated the general awareness of these risks wasn't really known in the industry or even to the regulators until much later. So that's why I'm a little concerned about the validity of some of these assumptions.
BY MR. SLATER:
Q. And I'm going to go through that with you a little more. But let me ask you this. I want to go back to what I was asking.
If you make the assumptions that I've asked you to make as to the inadequacy of the risk assessment, and if you make those assumptions, which you can assume those things are hypothetical as an expert as you know, and the risk assessment violated GMP, would it also be a violation of GMP to then manufacture with that manufacturing process which is creating NDMA?
MR. FOX: Objection to form.
A. Well, if we can be clear that I'm not accepting the assumptions, just viewing them purely as hypotheticals, then my

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answer would be yes. But I'm really not clear that the underlying assumptions are accurate at this point.
BY MR. SLATER:
Q. At the time ZHP developed the zinc chloride process, to your knowledge was any other API manufacturer for valsartan, or any other sartan for that matter, using the zinc chloride process in the world?
A. I don't know.
Q. Are you aware of whether or not there was any potential risk of the creation of nitrosamines with the original manufacturing process for valsartan, for the branded form of the drug, did you ever look to see whether or not that manufacturing process had a similar risk?
A. I did not because that would get into process chemistry, which is outside my area of expertise.
Q. Give me one second.
Sorry, I'm just digging through a pile because my goal in life is to not make the deposition last longer than necessary.

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Okay.
A. That's appreciated, sir.
Q. There's no reason to go longer than necessary.
MR. SLATER: Okay. Let's go, Chris, if you can do this, I want to go to what I think was marked Exhibit 209 previously, the IARC monograph from May of 1978.
(Whereupon, Chesney Exhibit Number 5 was marked for identification.)
BY MR. SLATER:
Q. It's probably going to take a moment because I just pulled something out of order. Look at that.
Okay. Mr. Chesney, have you ever seen -- and Chris could scroll up for you to show you what this is.
MR. SLATER: Maybe you could scroll up a little bit, show the bottom half also, or maybe make it fit the screen a little better. There we go.

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Q. And we can blow it up as you need, Mr. Chesney, whatever you need.
My first question is, have you seen this document, the IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Some N-Nitroso Compounds, Volume 17, dated in May of 1978? That's the date in the bottom left. Is this something you've seen?
A. No.
Q. And you can see it's marked with an exhibit sticker, Peng Dong ZHP 209.
Do you know who Peng Dong is?
A. The name is vaguely familiar, but I don't recall.
Q. Okay. I assume you're familiar with IARC?
A. I've heard of them. I'm not terribly familiar with them.
Q. The International Agency for Research on Cancer. That doesn't -- you're just generally familiar that they exist?
A. That's about it. I haven't had much to do with that agency over the years.

Q. You see that this is a component of -- at the top you can see the "World Health Organization." I assume you've heard of the World Health Organization?

A. Oh, of course, yes.

Q. And what I'm going to do, if we could, is go to page 36.

MR. SLATER: And let's blow up the third full paragraph. Good job. Thank you. Maybe a little smaller. Perfect.

Q. Can you see that okay, Mr. Chesney?

A. Yes, sir, that's fine.

Q. Okay. We're looking here on page 36 of this IARC monograph, the third full paragraph, it says, "It has been known since 1865 that the reaction of dimethylamine hydrochloride with sodium nitrate at an acidic pH yields N-nitrosodimethylamine," which is NDMA.

Do you see that?

A. Yes.

Q. Is this the type of feasible

scientific information you're talking about in terms of the ability of ZHP to have known that this reaction between the DMA that would be a degradant product of the DMF could react with the nitrous acid from the sodium nitrate and form NDMA? Is this the type of feasible scientific information you're talking about?

MR. FOX: Objection to the form. Beyond the scope of his report and the scope of his expertise, as he's testified to.

A. It's the sort of thing I would expect scientific experts with whom I would collaborate to take into consideration. By itself it is what it is, but it doesn't -- it doesn't go beyond what it says on its face. This tendency was identified a long time ago.

But it says nothing with respect to the process itself. I'd have to have somebody make that connection for me.

BY MR. SLATER:

Q. I understand. And I have a few different pieces to the puzzle that I'm planning to probably show you over the next

few minutes.

As far as what I just showed you, this shows that IARC, an arm of the World Health Organization, published as of 1978 that it's been known since 1865 that the reaction that ultimately created the NDMA has been known to scientists. That's what this shows, right?

MR. FOX: Objection to form. Calls for speculation.

A. That's what the sentence says.

MR. SLATER: Okay. Let's go now, if we could, to page 40. And we'll blow up that last paragraph. Perfect.

BY MR. SLATER:

Q. This says in part, "Most of the chemical and physical properties of the nitrosamines described in these monographs were taken from Druckrey et al," and cites to a 1967 publication. Then it says, and this is the part I wanted to really focus on with you, "The principal techniques employed for the analysis of volatile N-nitrosamines have

been described in a recent publication (Preussmann et al, 1978). The relative merits of high- and low-resolution mass spectrometry are discussed, since use of mass spectrometry as a confirmatory technique is particularly important."

Do you see what I just read?

A. Yes.

Q. So again, this is addressing the issue of whether or not analytical methods were available to actually detect the NDMA in 2011, 2012, and this is showing that as of 1978, it was being discussed in the World Health Organization publication that mass spectrometry was one available method.

Do you see that?

MR. FOX: Objection to the form, and incomplete recitation of the document.

BY MR. SLATER:

Q. Okay. You see that, right, Mr. Chesney?

A. I do.

Q. Okay. And again, this is the

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type of feasibly available scientific information that you were talking about earlier that you would expect ZHP's scientists to be aware of when they were doing their risk assessment, right?

MR. FOX: Objection to form.

A. It could constitute an informative data point, but it's by no means the entire picture.

MR. SLATER: Okay. Take that document down. Let's go now, Chris, if we could, to Exhibit 311, which is the publication Purification of Laboratory Chemicals.

Let me see if this has page numbers.

(Whereupon, Chesney Exhibit Number 6 was marked for identification.)

BY MR. SLATER:

Q. Okay. I've put on the screen a document titled Purification of Laboratory Chemicals, and you can see that it was marked as Exhibit 311 during the deposition of Min

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Li.

Do you see that on the screen?

A. I do.

Q. Do you know who Min Li is?

A. The name is familiar from ZHP documents, but I couldn't tell you what position she has, so that she --

Q. Or he?

A. -- as the case may be, occupies in the company.

Q. Okay. And just to be clear, you weren't provided the depositions of Peng Dong or Min Li as part of the materials you were provided, right?

A. I don't recall either of those, sir, no.

Q. Okay. And, for example, the IARC monograph I just showed you, that's not something you were provided, correct?

A. I was not.

Q. And this publication, the Purification of Laboratory Chemicals, which was used as a deposition exhibit with Min Li, that's not something you were provided

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either, correct?

A. I have not seen this document.

MR. SLATER: Chris, let's go to page 192 of this -- actually, stop don't go there yet. Let's go to the second page which has the publication dates. I just want to establish that.

Q. We can see that this has a first publication date of 1996 and reprinted in 1998, '99, and 2000.

Do you see that?

A. I do.

MR. SLATER: Let's go now to page 192. Perfect. There you go. You've got it, Chris. If you can blow up that bottom paragraph, and just read the first beginning. Just a tiny bit less because we're cutting off -- my picture cuts off. All right. Perfect. Thank you.

Q. You see that this references N-N-dimethylformamide, which is DMF.

Do you see that?

A. Yes.

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Q. And you understand that one of the changes to the manufacturing process when the zinc chloride process was created was to begin to utilize DMF. You're aware of that, right?

A. Yes.

Q. And this scientific publication, which we know was originally published in 1996 and reprinted up through 2000 on this copy that I am showing you, states that DMF "decomposes slightly at its normal boiling point to give small amounts of dimethylamine and carbon monoxide."

Do you see that?

A. Yes.

Q. And again, this would be the type of feasibly available scientific information you would expect the people at ZHP to have been aware of when they were performing the risk assessment with regard to their decision to add DMF to the manufacturing process, correct?

MR. FOX: Objection to form.

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A. It would be another data point that would have to be evaluated for its significance and context and understood fully, yes.
BY MR. SLATER:
Q. The fact that it was known in the scientific community that DMF could decompose to give off small amounts of dimethylamine is certainly something you would have expected the people at ZHP to be aware of when they were formulating and then performing a risk assessment on the zinc chloride process. You could agree with that, correct?
MR. FOX: Objection to form. Beyond the scope.
A. I would have no ability to form an independent expectation of that. That's the kind of thing I would ask the scientific expert, Is this something they ought to have known about, is this peer-reviewed research, was it -- did it have credibility, was it widely circulated. Those are all things that I would want to take into account to decide

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whether it's something that the ZHP folks ought to have known about.
It stands here as a single reference in an otherwise very lengthy document. I don't know who prominence it had in the industry at that time.
MR. SLATER: Okay. Chris, let's go to Exhibit 197, please.
MR. GEDDIS: Is there another exhibit number for that that you had too?
MR. SLATER: Possibly 14, it's the "N-N-dimethylformamide: much more than a solvent" in Tetrahedron.
MR. FOX: You're going to a different exhibit, Adam?
MR. SLATER: I am. The problem is Chris moved so quickly before, that now when he doesn't do something instantaneously we all say, What's going on?
MR. GEDDIS: What was it you said, 214?
MR. SLATER: 14, 1-4. It was

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definitely Exhibit 197 marked during Min Li's deposition.
MR. GEDDIS: 197. Found it.
(Whereupon, Chesney Exhibit Number 7 was marked for identification.)
BY MR. SLATER:
Q. On the screen we have an exhibit that was marked Exhibit 197 actually in the deposition of Peng Dong originally, I can tell you we also showed it to Min Li, and it's published in the medical journal Tetrahedron, or scientific journal I should say, and the title of this article is "N-N-Dimethylformamide: much more than a solvent?
Do you see that?
A. Yes.
Q. And this is dated in 2009. You can see it at the very top. Even though it's very small letters, it says "Tetrahedron," and the year is 2009.
A. Yes, I can see it.
Q. Great.

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MR. SLATER: Let's go now to the third page of this article, which is page 8315, please.
Q. It says in part, paragraph number 3, "Source of carbon monoxide. DMF decomposes slightly at its boiling point to afford dimethylamine and carbon monoxide, this reaction occurring even at room temperature in the presence of some acidic or basic materials. This observation has led to the use of DMF as a carbonylating agent."
Do you see that?
A. I do.
Q. Taken together with the textbook I showed you, and now I'm showing you a medical -- in a scientific journal, can you agree that, based on what I've shown you, it was at least scientifically feasible for -- and expected for ZHP to know that DMF could decompose or degrade and give off dimethylamine as part of this manufacturing process, that they at least had to take into account the possibility that that would occur?

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MR. FOX: Objection to the form. Argumentative, incomplete hypothetical.

A. I can agree that, from what you've shown me, that there are references in the scientific literature that are potentially useful data points that should be taken into account and considered in the overall scheme of things. But I'm not capable of judging them on the merits independently, so I don't know what relevance they really have.

BY MR. SLATER:

Q. What I'm just asking is, we can agree that the potential decomposition of DMF to give off dimethylamine, based on what I'm showing you, was something that you would expect ZHP to have at least been aware of as a potential chemical reaction as part of the zinc chloride process and take into account however they chose to?

MR. FOX: Objection to form.

MR. SLATER: Let me rephrase. I lost, because I was trying to finish

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the question and you objected. I'm not criticizing because I paused, but let me just ask again.

BY MR. SLATER:

Q. You would agree with me that you would expect that ZHP would have at least been aware of the potential degradation or decomposition of the DMF to give off dimethylamine, and to take that into account as something that could potentially occur during the zinc chloride process. Just limiting it to that, would you agree with me?

MR. FOX: Objection to the form. Asked and answered.

A. It's information that's out there in the scientific literature. It would have been appropriate for them to take a look at it and give it consideration.

MR. SLATER: Let's take that down now and go to Exhibit 211.

(Whereupon, Chesney Exhibit Number 8 was marked for identification.)

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BY MR. SLATER:

Q. Okay. We have on the screen an article titled Theoretical Investigation of N-Nitrosodimethylamine Formation from Nitrosation of Trimethylamine.

Do you see that?

A. Yes.

Q. And at the bottom of the first page of the article there's an exhibit sticker, Peng Dong ZHP 211. Again, I'm representing to you this was utilized in Peng Dong's deposition as well as Min Li's deposition, which we've already established you have not seen those transcripts, correct?

A. Correct.

Q. And the articles that I've shown you, these scientific articles that were used in those depositions, you haven't seen any of these, right?

A. No.

Q. Okay. Meaning I'm correct?

A. Yes.

Q. I wasn't trying to be picky, it's just sometimes the negatives on the

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double negatives won't be clear.

A. No, I have not seen this article before.

MR. SLATER: Okay. Let's, Chris, if you could just blow up the Introduction, that left column, that would be great.

Q. Okay. And let's just start out at the beginning. It says, "It is well known that N-nitrosamines are a class of undesired industrial and environmental pollutants, many of which are carcinogenic, mutagenic, and teratogenic. In particular, N-nitrosodimethylamine (NDMA), which is the simplest dialkylnitrosamine, has been demonstrated to be a potent carcinogen to various organs in animals, including liver, lung, and kidney." And I just want to stop there.

Does this comport with at least what you've learned about NDMA since you were retained in this matter, or from the literature, from the media reports you had seen before? I'm just curious if you're

familiar with at least these types of information about NDMA.

A. The carcinogenic potential, yes. The detail involving the specific organ systems that might be at risk, no, I haven't seen much in the way of specific reference to that before.

Q. And I neglected to ask about this, but maybe I can do it real quick.

The importance of detecting genotoxic impurities as potential manufacturing process impurities, that was not a novel concept in 2011, ZHP would have known at that point that that was something they had to be on the lookout for, right?

MR. FOX: Objection to form.

A. Be on the lookout for what?

BY MR. SLATER:

Q. For genotoxic process impurities as a part of any manufacturing process?

A. There's long been a general awareness that unidentified impurities need to be characterized so you know what you're

dealing with, and then back up and look and see what the implications are of those materials present in your product as a result of your process, and to the extent feasible to quantitate them.

Q. And with regard to genotoxic impurities which could potentially lead to cancer, it's been understood that those need to be focused on and they need to be identified and addressed, correct?

MR. FOX: Objection to form.

A. Well, if you identify either the potential or the actual occurrence of this type of impurity, then certainly it's important to understand it.

BY MR. SLATER:

Q. Looking now at the second paragraph under the Introduction, it says, "because dialkylnitrosamines are of great interest in carcinogenesis, much attention have been focused on their formation mechanism, especially from secondary amines. Consequently, NDMA is generally believed to be formed from the reactions of dimethylamine

(DMA) and nitrosating agents, such as N2O3, N2O4 and ONCl."

And I can represent to you that N2O3 would be nitrous acid, I believe. Actually I just screwed up the whole question so I've got to ask it again.

This says, "Because dialkylnitrosamines are of great interest in carcinogenesis, much attention has been focused on their formation mechanism, especially from secondary amines. Consequently, NDMA is generally believed to be formed from the reactions of dimethylamine (DMA) and nitrosating agents, such as N2O3, N2O4, and ONCl."

Do you see what I just read?

A. Yes.

MR. SLATER: And let's just scroll up a little bit just to the authors of the article again. I want to just show -- there we go.

Q. This article was published by three authors at the College of Life Science & Bioengineering at Beijing University of

Technology in Beijing, China, and it shows that it was -- in 2009 it was received, and published in 2010.

Do you see that?

A. Yes. Okay. I was just looking for publication date. Yes, I see that.

Q. Would you agree with me that this demonstrates that it was certainly feasible and expected for ZHP to be aware that the potential DMA that could be produced during the manufacturing process could react with the nitrous acid to form NDMA? Would you agree that this demonstrates that it's certainly something that they needed to be aware of and take into account in their risk assessment?

MR. FOX: Objection to the form. It's beyond the scope of his expertise, as he has testified repeatedly that he's not a scientific expert.

MR. SLATER: Counsel, do you want to testify?

MR. FOX: If you'd like me.

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MR. SLATER: We'll do that later. We do the lawyer testimony later.

A. This is another example of the kind of information I would need input from somebody with the appropriate expertise to fully take into consideration. I can only judge this on the merits.

BY MR. SLATER:

MR. FOX: Objection to the form.

MR. SLATER: Okay. I think we can take that one down.

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BY MR. SLATER:

Q. I'd like to ask you to assume that ZHP's corporate representative witnesses testified that they did not take into consideration the potential degradation or decomposition of DMF to yield DMA, nor did they take into consideration the potential reaction between DMA and nitrous acid, that they didn't even take that into consideration at all, they didn't think about it, they didn't look at the issue, they completely didn't think about that.

If my hypothetical is true, would you agree with me that that demonstrates a lack of rigor in violation of GMP based on them not even taking it into consideration and thinking about it?

MR. FOX: Objection to form.

A. I would not go that far until I had the opportunity to ask them a simple question, Why did you not, and hear what their justification is.

BY MR. SLATER:

Q. What if their justification was

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nobody knew -- rephrase.

What if their justification was, Nobody could have known that these chemical reactions could have occurred? In the face of what I've just shown you, would you agree that that would show that their evaluation fell below good manufacturing practices?

MR. FOX: Object to the form. Incomplete hypothetical.

A. I would then ask them why they took that position and what there is that's different about the chemistry of their process that leads them to conclude that.

BY MR. SLATER:

Q. What if they -- well, are you saying you would ask them why is it that you're concluding that nobody could have known about these potential chemical reactions in the face of publicly available scientific literature, including from scientists in Beijing, that you would not have known what other people had readily available to them?

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MR. FOX: Objection to the form.

BY MR. SLATER:

Q. I don't understand -- I'm just trying to understand why you would ask them that question in the face of what I've shown you.

A. I would -- no, I would expect them to know that that information was out there. But why they excluded it from consideration in their particular product would be what I'd like to hear their explanation of. I don't know if they would have such an explanation or not, but I would certainly ask them, Is there anything about your particular process that led you to believe that information such as this would not be relevant.

But a lack of awareness that it exists or even to rule it out as important, no, I would expect them to go that far at least.

Q. As a matter of GMP, right?

MR. FOX: Objection to form.

A. Yes.
BY MR. SLATER:
Q. What if their answer to your question was, We didn't exclude it, we never even thought about it --
MR. FOX: Objection to form.
BY MR. SLATER:
Q. -- would that fall below GMP then?
MR. FOX: Objection to form. Misstates -- or incomplete hypothetical.
A. They certainly should be looking at the relevant literature to see if there's anything about what they're proposing to do in their process that poses a potential risk. So yeah, I would expect them to at least be aware of the existence of this information.
BY MR. SLATER:
Q. And if their -- rephrase.
If their response to your question, which I think you said your question would be, Well, why did you exclude

this information from consideration, if their response was, We didn't even actively exclude it and say we're not going to consider it, we didn't even know it, because we didn't even do a research, a literature -- rephrase. Let me try to ask it clean.
If you were to ask them, Why did you decide this information didn't need to be taken into account, and they said, We didn't even make a decision about whether to take it into account, we just never even knew --
MR. FOX: Is that a question?
BY MR. SLATER:
Q. -- would I be correct that you would say, Well, your risk assessment fell below GMP because you at least should have known this information was available and made a reasoned decision as to how you were going to take it into account?
MR. FOX: Objection. Misstates testimony. It's also beyond the scope of his expertise, given that he's not a scientific expert.

BY MR. SLATER:
Q. You can answer.
A. It's a concern I would have, but I would ask that the scientific experts I was working with resolve it on a peer-to-peer basis and give me their insight and their opinion.
Q. Well, coming back to my question, though, since you've already agreed with me that they were required to at least know about these potential chemical reactions that could occur during the process, if you then asked them, Well, why did you not perform an actual risk assessment on whether or not these reactions were going to occur or were occurring, and they said, We never even took it into account, we didn't even think about this, we never even thought about these potential reactions, if that were to be their response, would you agree that that would show that their -- the fundamental parts of their risk assessment fell below GMP because they never even made themselves aware of these potential reactions to begin with?

MR. FOX: Objection. Beyond the scope, incomplete hypothetical, and misstates his prior testimony.
A. I'm sorry, I lost -- in all of that I lost the thread of the question. Can you restate it? I had to ask you to restate it, but please do.
MR. SLATER: Just so that I don't misstate it a little differently and get another objection that might distract you, Maureen, could you read that question back, please?
I'll ask the court reporter to read it back, and if I need to reask it I will again, but maybe this will be the quicker way to go.
(Whereupon, the reporter read back the following:
QUESTION: Well, coming back to my question, though, since you've already agreed with me that they were required to at least know about these potential chemical reactions that could occur during the process, if you

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then asked them, Well, why did you not perform an actual risk assessment on whether or not these reactions were going to occur or were occurring, and they said, We never even took it into account, we didn't even think about this, we never even thought about these potential reactions, if that were to be their response, would you agree that that would show that their -- the fundamental parts of their risk assessment fell below GMP because they never even made themselves aware of these potential reactions to begin with.)

MR. FOX: Same objection.

A. I would agree that the risk assessment would have been better had they taken that into account for sure.

BY MR. SLATER:

Q. Well, if they told you they never took it into account, that would violate GMP. You've already told me they were required to know about this scientific

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information, so if they didn't even consider it that would violate GMP, right?

MR. FOX: Objection to form. Misstates testimony.

A. I think that's taking the concept a bit far. But they certainly -- the risk assessment would certainly be improved by a thorough literature search, and if they missed something like this that was publicly available and directly involved the type of reaction that was involved in their process, then yes, it should have been taken into account. And if it wasn't, that would be a gap in the overall risk assessment.

BY MR. SLATER:

Q. It would be a gap in violation of GMP, correct?

MR. FOX: Objection to form.

A. Whether or not it's a violation of GMP I'm not been prepared to say without a more rigorous understanding of the scientific considerations here.

When you look at information like this in the literature, it may not have

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been created in an environment that duplicates adequately the environment that exists with respect to the process chemistry that you're dealing with, and there could be mitigating factors or things that would influence the production of NDMA in some way as to negate the risk. All that has to be taken into consideration before you can conclude what the impact of the lack of that information really was.

BY MR. SLATER:

Q. And what you just went through in terms of the types of questions that you might ask, you would expect that pursuant to GMP that people at ZHP would have asked themselves the same questions back at the time in 2011, right?

A. Yes.

MR. FOX: Objection to form.

A. That I can agree to. The question is whether in 2011 the technology was adequate to make that identification, and whether there was reasonable probability that they would even find anything if they looked.

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Those are the two basic questions that I would need the scientific support to answer.

BY MR. SLATER:

Q. Assuming the answer to both of those assumptions is yes, as I've asked you to assume in the hypothetical, if they didn't ask themselves those questions that you just recited for me about how you would take into account -- how to take this into account in their risk assessment, they didn't even go through that exercise, that would fall below GMP, right?

MR. FOX: Objection to form. Misstates testimony.

A. That would be a flaw in the overall risk assessment for sure, yes.

BY MR. SLATER:

Q. In violation of GMP, right?

MR. FOX: Objection to form.

A. I'm not prepared to go that far. That requires a multifaceted consideration really as to what the risk is that's presented.

If I may, GMP conceptually does

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not expect everything to be done perfectly. In fact, the regulations, the finished dose form regulations actually anticipate that imperfections will occur, and what it calls for is a thorough investigation when those imperfections do occur, not that everything be absolutely perfect every time.

If that were the case, no pharmaceutical products would be produced because nobody is ever 100 percent perfect. That's been my experience.

So the question really is not whether or not the risk assessment could have been better, the question is was it sufficiently flawed to violate GMP. And it's difficult for me to take it to that level.

I can certainly agree that this information you've highlighted would have been helpful, even should have been taken into consideration. But whether the fact that it was not, if the testimony indeed states that, constitutes a violation of GMP as a further analysis, that I would not be prepared to make based on this level of

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information.

BY MR. SLATER:

Q. If you were to assume that considering that information could have feasibly led to testing to see if nitrosamines were being formed, if you assume that, and that that testing would have shown NDMA was being formed, then the failure to take this into consideration in 2011 would be a GMP violation, correct?

MR. FOX: Objection to form.

A. If all that was true, yes. The problem is I've seen other information that suggests that, at least from the FDA's public statements, that suggests that that information was not -- or that technology was not up to speed until much later. Neither the regulators nor the industry at large really had that awareness.

So I question whether it was feasible in 2011. I don't know, and I would require the help of someone with the right scientific expertise to convince me of that.

If I could be convinced of that

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then, sure, I could get to the point of agreeing it was a violation of GMP, but not based upon bits and pieces of the total story.

BY MR. SLATER:

Q. When you were reading the information from the FDA, were you aware that the reason why nobody had been looking for NDMA before was because the manufacturing processes for valsartan hadn't created NDMA to the FDA's knowledge before the zinc chloride process was put into effect, and that that's how this issue came to the FDA's attention?

MR. FOX: Objection to form.

BY MR. SLATER:

Q. Were you aware of that?

A. Public statements allude to the timeline on this, and the reasons why it eventually did come to light.

What I remember from that as I sit here now is that full awareness and understanding didn't really occur until sometime in the middle of 2018. So I

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question whether it would have been something the company could have anticipated or known about in 2011.

Q. I read something in your report which indicated along the lines of what you've been telling me, that the FDA doesn't prescribe a one size fits all GMP approach to the manufacture of each product. I think you've been telling me that, right?

A. Yes, that's true.

Q. And I read a couple of things in your report, and I'm just going to run through them. One of the things you said is that the cGMP regulations describe what is to be accomplished, not necessarily how.

I think that's the same point, right?

A. Yes.

Q. And another thing you said is any reasonable format that achieves the desired results.

Again, that's another way of saying the same thing, right?

A. Yes.

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Q. And I think another place you said -- rephrasing.

Another part of your report on page 51 you said, As long as the approach ensures that the API meets its purported or represented purity and quality. That was another way of you saying you have to come up with an approach, it might not be the same approach someone else will have, but that's the outcome that you need to achieve, right?

MR. FOX: Objection to form.

A. Yes, I think in that -- sorry, Tom.

MR. FOX: Go ahead.

A. I believe in that case I was actually quoting an FDA compliance program to illustrate that point.

BY MR. SLATER:

Q. And that point would apply to what ZHP was doing in 2011 as part of its risk assessment, that its approach was required to ensure that the API met the purported or represented purity and quality of the API, correct?

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A. Yes.

Q. We know in retrospect that the risk assessment failed to do so, and that the API did not satisfy the represented purity and quality because it was -- it contained NDMA, correct?

MR. FOX: Objection to form. Calls for speculation.

A. I don't believe there was any specification established for NDMA at that point in time because there was no anticipation that it would be there.

BY MR. SLATER:

Q. That was due to the failure of the risk assessment to identify the potential creation of nitrosamines, correct?

MR. FOX: Objection to form.

A. In part.

BY MR. SLATER:

Q. When the valsartan was sold by ZHP, it was representing that it had a certain level of quality and purity, and listed what the ingredients and components were that were in those pills, right?

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A. I've never seen the labeling for how it was sold, nor any representations that were made to purchasers, but implicitly it would be required to comply with the law, certainly.

Q. Have you looked at the USP entries for the valsartan?

A. The monographs and the USP?

Q. Yes.

A. I don't recall that I looked at the monographs. I do have one USP citation in my list of references, but I don't think that was the valsartan monograph.

Q. You mentioned specifications before, and I think we can agree that, because we talked about it earlier, that one of the important parts of the risk assessment is to identify what are the impurities that need to be specified so that you can test to make sure they're below certain levels, right?

A. Yes.

Q. So if the risk assessment failed -- well, rephrase.

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We know the risk assessment failed to identify the potential NDMA impurity, we know that, that's why it was never part of the process validation testing, and that's why there was never any even attempt to set a specification for NDMA, right?

MR. FOX: Objection to form.

A. I think -- my understanding is that that's not the only reason.

The other reason is there were not available analytical methods that were sensitive enough at the levels that apparently this material was occurring to enable detection at that point.

BY MR. SLATER:

Q. And I think you said earlier you haven't seen Dr. Hecht's report, so you're not aware of the fact that one of the world's foremost experts regarding nitrosamines and the use of mass spectrometry has written in his report that the technical ability to identify the NDMA was absolutely available in 2011, that's not something that

you're aware of, right?
MR. FOX: Objection to form.
Lacks foundation, argumentative.
A. I'm not aware of it, no.
BY MR. SLATER:
Q. If I am correct that it was technically feasible for ZHP to have employed technology to test for NDMA and identify the NDMA in 2011, you would agree with me based on all the information I've shown you that they should have performed that test and they should have detected the NDMA before ever marketing this product, right?
MR. FOX: Objection to form.
Asked and answered, misstates testimony.
A. That would require a series of steps; that the risk analysis would recognize that as a potential problem, that they had the available technology or acquired it or found someone to contract with to do the testing, did the testing, and identified the NDMA at the levels in which it was occurring.
And even then, you would have

to take that quantitative information and determine whether or not that was a health risk, and if so, how severe, and to whom, and all the rest of it.
BY MR. SLATER:
Q. Well, we know what happened when the world found out there was NDMA in the valsartan, we found out that the levels that ZHP had created in its valsartan were so high that the pills couldn't be sold any longer, right?
MR. FOX: Objection to the form.
A. The levels were such that the FDA classified the recall as Class 2, which is minimal risk to health, and actually issued public advice to patients taking those tablets or capsules to continue to take the medication until they either had an alternative available, or their physician had switched their medication.
So the FDA's official advice on this was keep taking your medication until you have an alternative.

BY MR. SLATER:
Q. Are you aware that the reason the FDA said that is because they figured it's better not to have a heart attack or stroke in the next couple weeks while you go to your doctor and get a new drug rather than stopping the pill?
MR. FOX: Objection to form.
BY MR. SLATER:
Q. Let me reask.
Are you aware that the reason the FDA said that people should keep taking the pills until they can meet with their doctor is because there was a concern that people could suffer strokes or cardiovascular episodes and die, or have massive medical harm, and that they weighed that against the risk of taking the pills for another couple weeks while they get new medication?
You understand that's why the FDA said that, right?
MR. FOX: Objection to form.
A. A couple weeks or however long it takes.

BY MR. SLATER:
Q. Well, I mean, the FDA was making a decision, We don't want a bunch of people having strokes and dropping dead all over the place because they stopped taking their blood pressure medications while we get them onto other medications, and then the FDA -- shortly after that, this stuff was completely off the market, right?
MR. FOX: Objection to form.
A. It was off the market after the recall was conducted, yes.
BY MR. SLATER:
Q. Certainly the FDA telling people to keep taking the pills until they get an alternative blood pressure medication was not an endorsement of the safety of the valsartan, was it?
MR. FOX: Objection to form.
A. Safety is a relative concept in pharmacology. So it was a statement by the FDA that the greater good was served by patients continuing it until they could get an alternative medication.

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BY MR. SLATER:
Q. Was the FDA also concerned that because ZHP had such a massive part in the market that there could be a bunch of people left with no blood pressure drugs if they stopped taking it, and there could be a lot of people getting very, very sick and dying if they all stopped taking it right away?
MR. FOX: Objection to form.
BY MR. SLATER:
Q. Just asking if you know.
A. I don't know if they raised supply chain concerns or created a potential shortage.
Q. Let me go back to a question about the testing that you've talked about, of whether it was feasible to test.
If ZHP had actually taken into consideration the potential chemical reactions and realized that the creation of nitrosamines including NDMA was possible, and if it wasn't feasible to test for the NDMA or other nitrosamines back in 2011, wouldn't the proper thing to do at that point be to say,

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We can't move forward until we can test and confirm that these genotoxic impurities are not in this pill? Wouldn't that be what would be required if the testing didn't exist at the time?
MR. FOX: Objection to form.
Argumentative, beyond the scope.
A. If there was a concern about a substantial risk that they didn't have the feasibility to address through analytical procedures due to a lack of equipment or knowledge of the method or whatever, the usual approach is to try to find someone who can assist with that line of inquiry.
BY MR. SLATER:
Q. And I'm just going to play out what you've questioned me about to the end.
Let's assume that they -- there was no technology available to test for NDMA or other nitrosamines at that point, even though they knew this manufacturing process very well could be creating these genotoxic impurities, if that were the case -- I'm taking your hypothetical -- if that were the

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case, then they would not be able to manufacture by that process, they would have to come up with a different way to manufacture it where there wouldn't be the potential creation of a genotoxic impurity that you couldn't test for, correct?
MR. FOX: Objection to form.
A. That's a possible outcome.
BY MR. SLATER:
Q. That would be the -- I'm sorry, I missed your answer because I think you might have broken up.
A. I'm sorry, just waiting for Tom.
That -- yes, that would be a possible outcome. They could elect to hold off on the process change until that question could be answered, yes.
Q. I mean, that would be -- rephrase. That would be required -- rephrase.
At the very least, they couldn't go forward and institute that manufacturing process until they could answer

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the question of whether or not this genotoxic impurity was in the pill, right?
MR. FOX: Objection to form.
Incomplete hypothetical.
A. They should have taken that into consideration, and that's a decision that would have to be made in light of all the facts, and with the appropriate scientific expertise coming to bear.
But yes, that's a possible decision that they could have taken at that time, to not go forward.
BY MR. SLATER:
Q. It would not have been -- rephrase.
Taking your hypothetical that there was no test in existence that could have told you whether or not this genotoxic impurity was there or not, if that was the fact, it would not have been acceptable to go forward with the manufacturing process while not knowing if there was going to be this genotoxic impurity. That would not have been permitted, correct?

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MR. FOX: Objection to form. Beyond the expertise, incomplete hypothetical.
A. Again, I would agree if and only if the weight of the science argued that there was a significant risk of formation of NDMA. There are literature references which you've shown me that showed in a laboratory setting people that identified this as a potential risk that's of concern, they should consider that.
But it would take a more wholistic assessment to understand whether that was a real risk, and decide accordingly whether to proceed with that process change at that time.
BY MR. SLATER:
Q. In retrospect you would agree with me it was a real risk because it happened, right?
MR. FOX: Objection to form. Argumentative.
A. Well, I agree with you that it happened.

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BY MR. SLATER:
Q. Okay. I wanted to just establish that. If we -- if you'll assume for the moment that a reasonable scientific expert in this field would say, Yes, this would be considered a real risk that this manufacturing process could create NDMA or other genotoxic impurities, if that were the fact, and if your hypothetical was correct that no test existed that could have measured whether or not this genotoxic impurity was actually being created, under those circumstances you could not go forward and manufacture with this process, you'd have to come up with a different way to do it, right?
MR. FOX: Objection to form.
A. You should not go forward unless there's a persuasive reason to believe that the formation of these impurities would be at such a low level that it would not present a risk to human health.
MR. FOX: Break, Adam?
MR. SLATER: Sure. I was losing track of the time. It's fine.

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BY MR. SLATER:
Q. Do you want to -- I don't know what you want to do, Mr. Chesney, if you want to take a little longer, you want to eat because it's almost 1:00 o'clock, whatever you want?
A. Well, maybe a little bit longer and just grab something quick. I'm certainly not one who takes a big lunch anyway.
Q. All right. Well, you tell me, how long would you like? I'm just on my second bite of my apple so far, so I'm going to eat an entire apple for the next eight hours.
A. Okay. Well, it's about 20 minutes of 1:00, why don't we say, I don't know --
Q. I'm not trying to rush you. Make sure you give yourself a comfortable amount of time.
A. Ten minutes past 1:00 sound okay to you?
Q. That sounds really good. We'll shoot for that.

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A. All right. Fine.
THE VIDEOGRAPHER: The time is 12:38 p.m. We are off the record.
(Whereupon, a luncheon recess was taken.)

AFTERNOON SESSION

THE VIDEOGRAPHER: The time is 1:24 p.m. We are back on the record.

BY MR. SLATER:

Q. Okay. We are ready to resume, Mr. Chesney.

Question, I read your discussion of adulteration in your report, which I hope not to have a long, drawn-out discussion about it, I think I understand your points, but we may have to come back to it a little bit. But let me ask you one question maybe to help to avoid a lot of that. So here's the question.

If the zinc chloride process violated cGMP as we've discussed, if that's the case, then the valsartan API manufactured with that process would be adulterated, correct?

MR. FOX: Objection to form.

A. If it is determined that there is a GMP violation that is sufficient to establish adulteration under the FDCA.

That's a big if.

BY MR. SLATER:

Q. I understand. Nobody is saying that you've agreed to all aspects of the hypothetical I gave you, but I just wanted to understand if that's the case what the consequences were, or what the implications were.

And sort of -- okay. What I'm doing is looking at my outline to see if I can cut through a few things. Okay.

We talked a little bit about earlier about what ZHP did when they learned about the NDMA in the valsartan. I want to talk a little more about that with you, okay?

A. Okay.

Q. Let me just find in your report.

One of the things that you said in your report is the actions taken -- well, let me start over.

With regard to what ZHP did when it learned that there was NDMA in the valsartan, you say -- this is on page 40 of

your report, "The actions taken are, in my opinion, responsible steps that the FDA would expect of any company who had discovered and self-disclosed an issue with a distributed product."

I want to ask you a couple questions about that statement, okay?

A. Sure. That's on page 40. Can you tell me, I've got page 40 open on my hard copy, whereabouts are you in that?

Q. The third line from the top.

A. Oh, okay. All right. I see it, yes.

Q. When you say that those were responsible steps that the FDA would expect of any company in that situation, those steps were legally required of ZHP, correct?

MR. FOX: Objection to form. Calls for a legal conclusion.

BY MR. SLATER:

Q. I'll ask the question differently.

Based on your understanding of the applicable FDA regulations and statutes,

is it your opinion that those steps that ZHP took in June of 2018 were legally required of ZHP?

MR. FOX: Same objection.

A. No. These are not things that are covered by any specific FDA regulation or statutory requirement; they're just reasonable and proper things to do when a company has information of this sort.

But there's nothing that I'm aware of that's an affirmative duty for ZHP to have done any of these based on a specific FDA regulation or statutory requirement.

BY MR. SLATER:

Q. One of the things you told me, and it's stated in your report, is that pursuant to 21 CFR 314.81(b)(1), ZHP was required to submit a field alert report within three business days to the FDA once it had learned that there was NDMA in the valsartan, correct?

A. But that's not one of the five elements that I cite here. It begins on page 39 at the bottom.

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Q. Okay. So let's go through the five elements. Well, going back to -- I'll ask you a different question and then we'll come back to where you were.

ZHP was legally required pursuant to 21 CFR 314.81(b)(1) to submit a field alert report to the FDA within three business days of learning there was NDMA in its valsartan, correct?

A. Yes, with one slight modification, and that being that because this is under an abbreviated new drug application, the regulation that directly covers it is 314.98, but it reflects back to 314.81 for the content. So in effect, yes.

Q. Bottom line was ZHP was required to notify the FDA that there was NDMA in its valsartan within three business days of learning that, correct?

A. Yes.

Q. Once ZHP knew that the zinc chloride manufacturing process was creating NDMA as an impurity, was ZHP required to stop using that manufacturing process as a matter

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of GMP pending further evaluation?

MR. FOX: Objection to form.

A. Once again, no specific requirement for that, but that would be the reasonable thing to do.

BY MR. SLATER:

Q. Well, it's my understanding that at all times that ZHP was manufacturing valsartan with the zinc chloride process, that if it knew that NDMA was an impurity in that valsartan API, that ZHP would have had to address that situation pursuant to GMP, correct?

MR. FOX: Objection to form.

BY MR. SLATER:

Q. Starting broad right now.

A. What do you mean by "address that situation"?

Q. Well, let me ask you this question.

When ZHP first learned that there was NDMA in its valsartan API and that it was a process impurity, did GMP require that ZHP take any steps?

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MR. FOX: Objection to form. No foundation.

A. It would require that they conduct a thorough investigation to determine where that was coming from, and how to control it going forward, and what to do about it in the interim.

BY MR. SLATER:

Q. When you say how to control it in the interim, what do you mean by that?

A. Well, the steps that they took, for example, placing existing inventory on hold until the investigation was complete and the decision could be made as to what to do. Ultimately, of course, they conducted a recall, notifying customers to place a hold on valsartan API, those kinds of interim controls, while the investigation is ongoing and coming to its ultimate conclusion. Those are reasonable things to do.

None of those are prescribed specifically by GMP, but they certainly are the kinds of things that responsible companies do when in this situation.

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Q. Well, what I'm trying to understand is what GMP required based on the documents you reviewed, based on -- to the extent you have any knowledge of any internal SOPs, I'm trying to get a idea of what GMP required when ZHP first learned that there was NDMA in its valsartan API.

I think the first thing you said is it needed to do a thorough investigation to figure out why, where it's coming from, correct?

A. And also the risk. And then --

Q. I'm sorry, I wanted to go one step at a time just because --

A. Sure.

Q. I'll start over. We'll do it in small steps.

A. Okay.

Q. When ZHP first learned that there was NDMA in its valsartan API, GMP would have required ZHP to do an investigation to determine why is it there, where is it coming from, correct?

A. Yes, and the associated risk.

Q. And to evaluate the associated risk?
A. Yes.
Q. Once ZHP understood that this was coming from the process, the manufacturing process itself, and understood that this was a genotoxic impurity that was considered to be a probable human carcinogen, what did GMP require ZHP to do once it knew that information?
MR. FOX: Objection to form.
A. If feasible, quantify the levels of the compound that were present as a result of its formation during the process, and include a health hazard assessment as to what the implications are of that level of material, once they had a clear understanding of what the levels were that were occurring, whether they were just trace levels that would perhaps have a negligible or no effect, or whether they were at levels of concern. That would be the next step.
BY MR. SLATER:
Q. You would agree with me that

knowing what you know now, the levels were at levels that would be of concern, correct?
A. Right. And they agreed as well, that's why they conducted the recall.
Q. And again, I'm sticking with GMP right now, so I want to just make sure we're on the same page that once ZHP understood there was NDMA in the valsartan API, it needed to do a thorough investigation, determine what was the root cause, also to evaluate the potential health hazard, quantify the levels.
And then what else would have been required by GMP?
MR. FOX: Objection to form.
A. Exactly what they did here, which is for the quality unit to take appropriate action with respect to the material in their possession, and would have to evaluate whether a recall was necessary, which they did. And they placed the material on hold and notified their customers. They also notified the FDA.
///

BY MR. SLATER:
Q. Would that also have required that they stop manufacturing for the time being?
A. It wouldn't have required that. Some companies in a situation like this where information is still developing and they're not sure where it's going to come out, if there's sufficient demand they may continue to manufacture at risk, but put any new lots manufactured also on hold.
Other companies will look at that and say no, the risk is too high, we don't want to make that investment in the cost of goods, and they'll simply cease manufacturing until they sort the matter out.
So if they continue to manufacture, they should certainly -- they would certainly not be wise to distribute any additional product made, but rather to put that on hold with the rest of it.
Q. Would there have been anything else that GMP would have required of ZHP?
MR. FOX: Objection to form.

A. Once a final conclusion is made that the product is not in a saleable condition, then the final thing would be for the quality unit to reject the material that they still had control over and any returns they get back as a result of the recall.
Some companies in a recall situation will authorize the destruction by their consignees rather than have it all returned.
BY MR. SLATER:
Q. And your understanding is that from all the things you've seen, that ZHP first learned that there was NDMA in its valsartan in June of 2018, is that correct?
A. That's when the investigation was in its final or latter stages, and they had done some quantification, yes.
Q. Did you come to an understanding of how -- well, rephrase. Did you have an -- rephrase.
Did you review materials having to do with the interactions between Novartis and ZHP regarding the NDMA impurity in the

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valsartan which led to the disclosure?
MR. FOX: Objection to form.
A. I do recall reviewing some of the original reports, or an original report from Novartis that they had detected an unidentified impurity.
BY MR. SLATER:
Q. Did you notice that it was Novartis and a third party lab that Novartis retained that identified the NDMA before ZHP did?
A. I don't recall specific details. It's possible that I did, yes.
[redacted]

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[redacted]
in

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your report. That was not something you actually addressed in your report, correct?
A. I don't recall addressing it.
Q. Do you have any opinions as to whether -- rephrase.
I didn't see any opinions in
[redacted]
opined on, correct?
A. I don't believe I dealt with that specifically in my report.
Q. You would agree that when ZHP was receiving complaints from its customers of unknown peaks on chromatography that ZHP had certain GMP obligations in response to those complaints? We'll get to what those responsibilities were, but you would agree that that would trigger certain GMP responsibilities, correct?
MR. FOX: Objection to form. Foundation.
A. Yes, they should investigate

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those complaints for sure.
BY MR. SLATER:
Q. They would have been required by GMP to conduct a risk assessment with regard to those peaks in an effort to -- well, let me ask it differently. Maybe I won't use the word risk assessment, and you'll tell me, it could be something else closely akin.
When ZHP was -- rephrase.
When ZHP received the customer complaints of these unknown peaks in the valsartan API, GMP required ZHP to analyze and try to determine what those unknown peaks represented, correct?
MR. FOX: Objection to form.
A. When you use the word "analyze" there, can you be more specific?
BY MR. SLATER:
Q. Well, sure.
ZHP would have been required to try to learn the reason why those unknown peaks were appearing, correct?
A. Yes. And that could be through

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dialogue with the complainant, review of information submitted by the complainant, review of production records, a variety of ways, sometimes including laboratory analysis of retained samples if that's appropriate. All of that has to be taken into consideration based on the details of the complaint.

Q. One of the things ZHP would have been expected to do would have been to evaluate the manufacturing process to determine whether there was the potential creation of impurities that could explain those unknown peaks, correct?

MR. FOX: Objection to form. Calls for speculation.

A. Once the manufacturing process is established and being followed, there's no requirement that they go back and reconsider something like that.

What they would need to do instead is to make sure the batch records reflect that the manufacturing process that was used for the batch that was the subject

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of the complaint was followed as required by the master form of the record.

BY MR. SLATER:

Q. In terms of deciding what testing to -- rephrase.

One of the things ZHP had to do was determine what type of testing to perform to try to determine the explanation for those unknown peaks; that would have been part of what they should have done, correct?

MR. FOX: Objection to form.

A. They should have determined whether testing was even feasible or necessary, because sometimes the information that comes in from the complainant is not that you don't really need to go to testing, other times it's helpful. So it depends on the details.

BY MR. SLATER:

Q. Well, in retrospect we know that there were unknown peaks attributable to NDMA, and that certain testing would have disclosed the presence of NDMA. We know that in retrospect, right?

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MR. FOX: Objection to form.

A. I'm not sure that I know that at all. First of all --

BY MR. SLATER:

Q. Was it in the materials you reviewed?

A. From the public statements by the FDA, those analytical procedures were not fully robust until a later date for one thing, you know. So I don't know what was available at the time. We've talked about these literature references and so on.

But again, this is something I would ask a subject matter expert, Was there analytical technology available that should have been used, could have been used under these circumstances to shed some light on this.

But the ordinary approach with unknown peaks is to attempt to identify them qualitatively, and then once you know that, quantitate them if that's possible with existing technology.

Q. When you say "qualitatively,"

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you're talking about figuring out what they are?

A. Yeah, what is it. And then quantitatively is okay, how much is it, how much is there present, what level is it at.

Q. Well, one of the things that ZHP would have had to question was, Is there a test we can perform to identify the source of those unknown peaks. They would at least have been expected by GMP to ask themselves that question, right?

MR. FOX: Objection to form.

A. What I have seen the scientists do is look at the unknown peaks, look where they're alluding, evaluate the size and occurrence of them, and attempt to infer from that what might be going on.

If additional testing is necessary, then they do that, but I'm not the one to make that call.

BY MR. SLATER:

Q. I read somewhere, and I don't remember if it was in your report or in some of the ICH documents, that risk assessment is

not a static process, it's a process that continues through the lifecycle of the drug's production and manufacture, is that correct?

A. I would agree with that statement, yes.

Q. So when the unknown peaks were brought to the attention of ZHP, one of the things that would have been prudent for them to do would have been to go back to their risk assessment to determine whether it was adequate to make sure they hadn't missed something that could explain those unknown peaks. That would have been a prudent step, right?

MR. FOX: Objection to form. Calls for speculation.

A. I don't know if they did that or not, but they certainly could have.

BY MR. SLATER:

Q. It would have been prudent for them to do so, correct?

MR. FOX: Objection to form.

A. Yes.

///

BY MR. SLATER:

Q. And if it was scientifically feasible for ZHP to have evaluated the manufacturing process, gone through the chemical reactions that could have been occurring, and identify that potentially nitrosamines were being created, and if it was technically feasible to perform a test like mass spectrometry to determine whether these were nitrosamines causing these unknown peaks, if both of those ifs -- if the answer is yes to both of those, then that would have been expected by ZHP, that would have been expected by GMP, correct?

MR. FOX: Objection to form. Incomplete hypothetical.

A. That's the sort of question I would turn to a subject matter expert to help formulate.

BY MR. SLATER:

Q. I'm asking you to assume the answer is yes, it would have been scientifically feasible to figure out that these reactions could have led to the

creation of nitrosamines, and I'm asking you to assume that testing, including mass spectrometry, was available to test to see if this was a nitrosamine peak, if the answer to both of those is yes, then GMP would have required ZHP to do so when those unknown peaks were reported, correct?

MR. FOX: Objection to form.

A. There's a lot of ifs in that hypothetical.

BY MR. SLATER:

Q. Is the answer yes?

A. The answer would be yes, if the answer to all the ifs you just posed was also yes.

Q. So again, this comes back to the importance of identification of the potential impurity being the trigger to many of these cGMP functions, correct?

MR. FOX: Objection to form.

A. Yes.

BY MR. SLATER:

Q. Would you agree that as soon as ZHP had internally determined that those

unknown peaks could be due to the formation of a nitrosamine as a result of the manufacturing process, that ZHP was obligated to tell the complaining customers that based on their analysis of the manufacturing process, one explanation could be nitrosamines?

MR. FOX: Objection to form. Calls for speculation, incomplete hypothetical.

A. There's no requirement for them to notify the complainant at that stage of the game. They're in the middle of an investigation. They have a hypothesis formed, as you've described it, they're putting a hypothesis to the test, so their main investigation, that would probably be a premature point at the time.

BY MR. SLATER:

Q. Once ZHP actually tested its hypothesis and confirmed that there was NDMA forming in the valsartan as a result of the manufacturing process, at that point was ZHP required to notify its customers?

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MR. FOX: Objection to form.
A. Required, no. Prudent, yes.
BY MR. SLATER:
Q. How about a customer that had complained and said, Please tell us what these unknown peaks represent, was ZHP required to tell those complaining customers once ZHP knew it was NDMA, that yes, those peaks were due to NDMA?
MR. FOX: Objection to form.
No foundation.
A. Not required by GMP, but again, the sort of thing that prudent companies do, and in fact ZHP did in June of 2018.
BY MR. SLATER:
Q. If ZHP knew that there was NDMA in its valsartan API and continued to sell the API and didn't tell any of its customers and didn't tell the FDA, that would be inexcusable, correct?
MR. FOX: Objection to form.
No foundation, argumentative, beyond the scope.
A. Use of the word "inexcusable"

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is a little inflammatory. I think if they had knowledge that a product posed a danger to health and didn't do anything about it, that would certainly be inappropriate, and they could potentially be in violation of the Act for other reasons other than GMP as well.
BY MR. SLATER:
Q. What could they potentially be in violation of under the Act, aside from GMP?
A. If --
MR. FOX: Objection to the form. Calls for a legal conclusion.
BY MR. SLATER:
Q. You can answer.
A. Okay. If they are aware that a product contains a contaminant that poses an actual or potential danger to health, and tell no one and continue to ship it anyway, that could be construed later, after evaluation of all the facts, as having shipped a contaminated and, therefore, adulterated product in interstate commerce.
Q. What are the consequences for

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that?
MR. FOX: Objection to form.
Calls for speculation.
A. Well, any of a number of consequences. It would depend on a variety of factors.
A product can be seized. If it's domestic US channels of distribution, FDA can move for that.
FDA can seek an injunction to cause a company to cease and desist violative conduct.
They can deal with it as they did in this case with a warning letter, which is a lesser way of handling it.
There are a number of other possibilities, depending on the circumstances. And whether it's in domestic commerce or coming in from abroad would change the equation as well.
BY MR. SLATER:
Q. Well, here we're talking about API that was coming in from China.
A. Right.

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Q. If it turned out that ZHP knew that its zinc chloride manufacturing process was creating NDMA in the API, and ZHP despite that knowledge continued to sell the API and not inform any of its customers or any regulatory authorities and kept that knowledge secret and did so for months, that would be a violation, I would assume, of the Food, Drug, Cosmetic Act, correct?
MR. FOX: Objection.
Hypothetical, no foundation.
MR. SLATER: You know what, Counsel, you can have your -- you have your standing objection, because you give it to every question, I'm not going to make you keep saying it. I want to just get through this.
MR. FOX: It's beyond the scope of his opinion.
MR. SLATER: I'm not so sure it is.
A. Okay. Once again let's be clear on what the question is, Mr. Slater.
MR. SLATER: I'm going to ask

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Maureen, if you could read it back. It worked well the first time, so try the second time.

(Whereupon, the reporter read back the following:

QUESTION: If it turned out that ZHP knew that its zinc chloride manufacturing process was creating NDMA in the API, and ZHP despite that knowledge continued to sell the API and not inform any of its customers or any regulatory authorities and kept that knowledge secret and did so for months, that would be a violation, I would assume, of the Food, Drug, Cosmetic Act, correct.)

A. One thing that's missing from the fact set that you put forth is how much of the NDMA is present, whether it's at miniscule trace amounts or amounts that could potentially pose a hazard to health, and that would be necessary for me to give an opinion.

I would also need to know once the amounts were quantified what the medical

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opinion is in terms of the health hazard that would be necessary. Because if something is present at very minuscule trace amounts that pose no risk whatsoever, then that could result in a different answer.

BY MR. SLATER:

Q. Do you know the amounts that were found in ZHP's API? Did you have a chance to see that?

A. I have.

Q. Those amounts.

MR. FOX: Object to form.

A. Yeah, those amounts are concerning. And again, there are a lot -- a string of ifs in a row here. If this was going on, if they were fully aware of it, if they didn't notify the FDA, if they didn't notify their customers, if they continued to sell it, and so on, then yes, that could be construed as a violation of the Food, Drug & Cosmetic Act. I don't want to give a legal opinion here.

The fact is, as my report relates, that's not what they did in 2018.

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BY MR. SLATER:

Q. When you say that could be a violation of the Food, Drug, Cosmetic Act, could that be something that could rise to the level of being criminal?

MR. FOX: Objection to the form. You're asking him for a legal opinion.

MR. SLATER: He's your expert who cited to regulations all over the report. I think he's competent to talk about the legal implications of the conduct of your client.

MR. FOX: And I think he did that in the report. You have my objection.

MR. SLATER: I appreciate it.

BY MR. SLATER:

Q. You can answer.

A. Any decision to go forward with a criminal prosecution would go even beyond the scientific multidisciplinary process that I mentioned. This is hence my reluctance.

[redacted]

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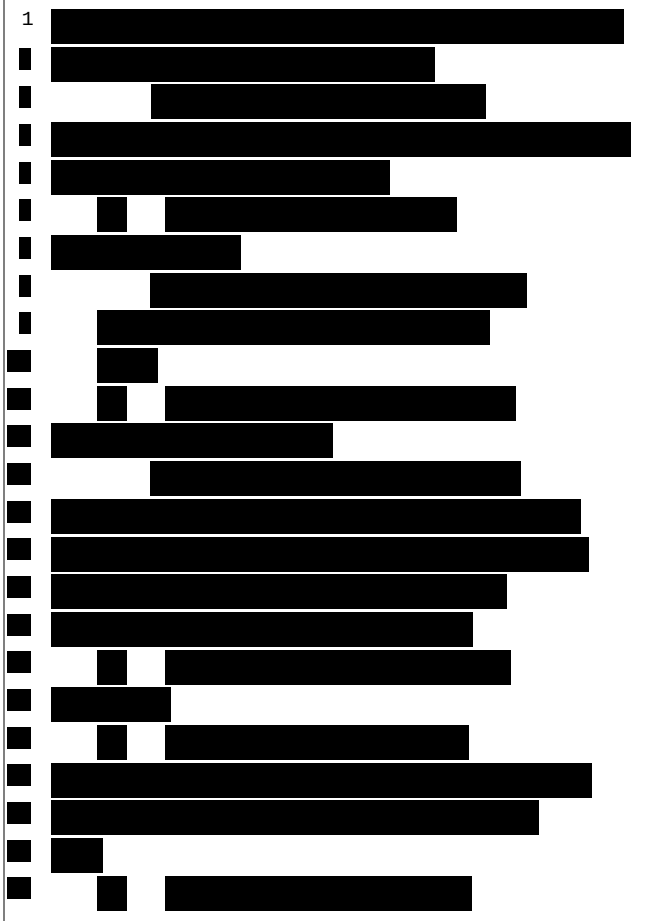
[redacted]



Q. Okay.

MR. SLATER: Let's go to the next page, please, Chris.

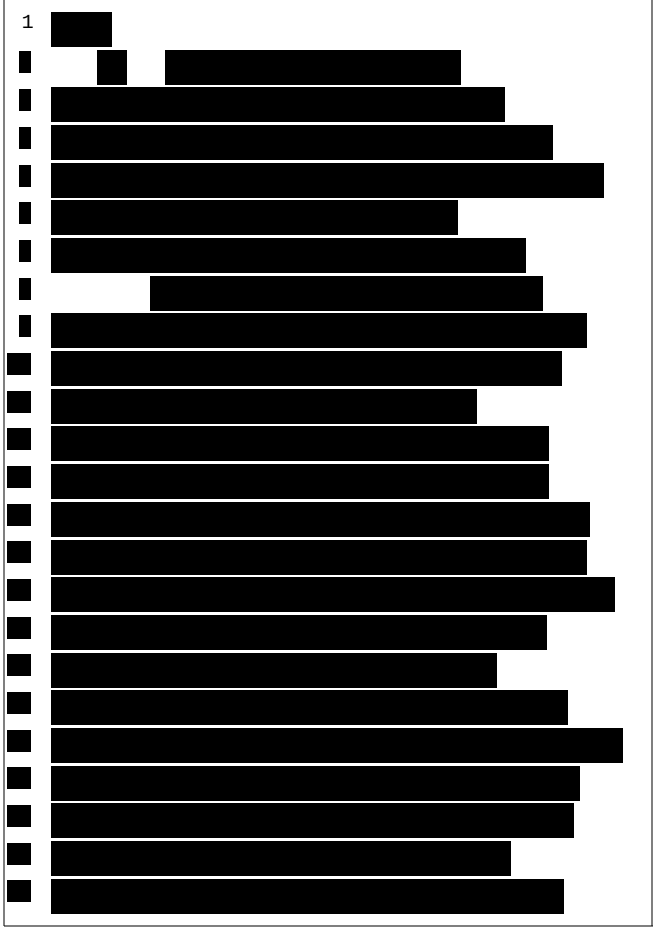
MR. FOX: Is there a date on this, Adam?

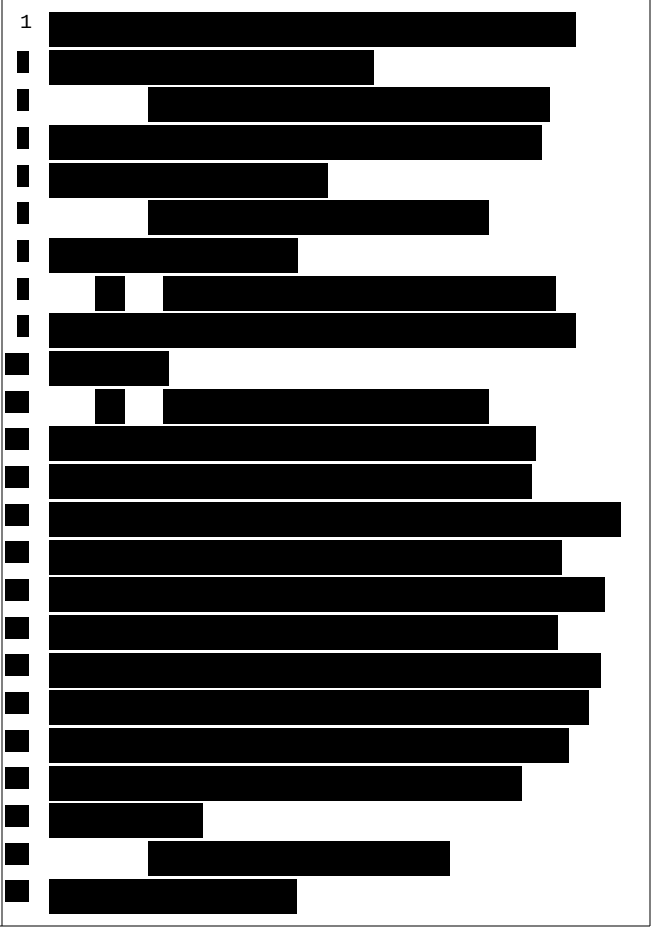
MR. SLATER: Is there a date on this. I believe I can get that for you. I don't remember that off the top of my head.

MR. FOX: Okay.

MR. SLATER: But we can get that and we'll certainly make a record of it. It was used in a prior deposition, so it's certainly been identified in the metadata.

BY MR. SLATER:





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[redacted]

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[redacted]

another exhibit which will be, I believe, 296.

(Whereupon, Chesney Exhibit Number 10 was marked for identification.)

MR. SLATER: Chris, I want the translated version of this, not the Chinese version of the e-mail.

A. Can we pause on that PowerPoint for just a moment?

BY MR. SLATER:

Q. Sure, we can go back to it.

A. I just have a question.

[redacted]

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[redacted]

A. From my experience when you go from Chinese to English, sometimes things don't come across quite the same way.

Q. Fair enough.

A. I've dealt with Chinese companies in the past, and sometimes things are a little hard to follow in the translated version.

Q. No problem.

Let's go back to Exhibit 296 now.

Now, I'm showing you an e-mail marked as ZHP 296 which was sent by Jinsheng Lin, Ph.D who we just read about in that CEMAT PowerPoint. And do you see his name there at the top?

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A. Yes.

Q. And it was sent to a number of people, Jucai Ge, Tianpei Huang, Wangwei Chen, Wenquan Zhu, Wenbin Chen, Mr. Li, Peng Dong, Lihong Lin, Yanfeng Liu, Peng Wang, and Wenling Zhang.

Do you see that?

A. I do.

Q. And the date of this e-mail is July 27, 2017. Do you see that towards the top of the e-mail?

A. Yes.

Q. And what I want to do is go through first, this is -- the first person it's sent -- rephrase.

It's addressed to Ms. Ge. As you can see, it says, "Ms. Ge: According to the results of our telephone communication with the Technology Department at Chuannan Plant today," and then it talks about "the incomplete quenching of sodium azide caused by the separate treatment of irbesartan sodium azide wastewater," and it goes into that area, it discusses that.

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Do you see that?
A. Yes.
Q. Okay. What I would like now to do is go to -- now, looking at the bottom of that paragraph, Dr. Lin points out, "However, after the improvement, there is an unknown impurity of about 0.544 percent at 26 minutes in the crude irbesartan, and it is the largest impurity in the irbesartan crude product."
Do you see that?
A. Yes.
[redacted]
MR. SLATER: Let's go now to the next page, please, Chris, the top of the second page.

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Q. At the top of the next page Dr. Lin states, "Through the secondary mass spectrometry analysis, it can be inferred that the extra NO substituent is in the cyclic compound fragment, and it is very likely that it is an N-NO" -- which would be an N-nitroso -- "compound; it is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite, and its structure is very toxic." Then it says, "Its possible formation route is shown as follows:"
Do you see what I just read?
A. Yes.
Q. Were you aware before right now that at least as of July 27, 2017, ZHP knew internally that there was NDMA in valsartan, and that the mechanism that was creating it occurred when the valsartan was quenched with sodium nitrite during the manufacturing process?
MR. FOX: Objection to the form. Misstates the document.
A. I can't conclude that based on

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what you've read up to this point in time.
BY MR. SLATER:
Q. Okay. This e-mail is dated July 27, 2017.
A. No, the date is not in question. But I can't conclude from what I've heard so far that this suggests that this material is actually in finished valsartan.
It talks about being in crude irbesartan, and at some stage of production in valsartan. I have no idea how much more synthesis or purification either of those compounds are supposed to go through as they're being manufactured and whether that would remediate this or not.
That's exactly the kind of scientific analysis that I would defer to others and would require collaboration on.
Q. Okay. I hadn't asked a question at that point, but I appreciate you telling me where you wanted to take this. But let me go back now to what I want to ask you.

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This e-mail is dated July 27, 2017. It's written by Jinsheng Lin, who we [redacted]
We went through that just a few moments ago, correct?
A. Yes.
[redacted]

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[redacted].

Q. What I'm asking you is -- so we've established that. Now let's go to my next question.

In this e-mail Dr. Lin, whose responsible was to understand and discover such root causes, states that what was being seen in the irbesartan "is similar to the NDMA that occurs in valsartan when it's quenched with sodium nitrite."

Do you see that? Just asking if you see those words.

A. I do.

[redacted]

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[redacted]

Q. And in this e-mail, Dr. Lin compares what is being seen in this irbesartan that they're experimenting with and says that what they're seeing is similar to the NDMA that occurs in valsartan when quenched with sodium nitrite. He's stating a comparison to what -- according to the words on this page -- what he knows to occur in the valsartan when it's quenched with sodium nitrite, which you'll agree with me is a true statement because that was the ultimate root cause ultimately disclosed to the world, correct?

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MR. FOX: Objection to form. The document speaks for itself.

A. I'm still not certain about the timeline here, but I mean, it says what it says. So certainly I'm not quarreling with the fact that the words are there.

But whether that aligns to what the other documents I reviewed say in terms of when that determination was made, my memory is the final determination that they based the recall on was not made until 2018, which would have been approximately a year more or less after this was done.

So I'm not sure when the gentleman makes this statement whether he's basing that on a final conclusion, a speculation, a work in progress, or what that is. It says what it says.

But beyond that, I don't know.

BY MR. SLATER:

Q. Well, you know from the materials you were provided that what he says here is the root cause for the creation of NDMA.

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A. Was eventually determined to be.

Q. Okay. And he was speaking to the root cause in July of 2017. That's what it says right here, right?

MR. FOX: Objection to form. The document speaks for itself. Stop trying to put words in his mouth.

BY MR. SLATER:

Q. That's correct, right, Mr. Chesney?

A. It says what it says.

Q. You were not shown this document or told about this e-mail by the people who retained you, is that correct?

A. This is the first time I've seen it.

Q. And you saw the list of people on the first page that this was sent to. So this was not one person hoarding this information; it was shared with multiple people within the company. I showed you that, correct?

A. You showed me the list that it

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was supposedly sent to, yes.
Q. If ZHP knew, as reflected in this document, that there was NDMA in valsartan as of July 2017, all the things that you said that ZHP was required to do in June of 2018, you would say all those things were required to be done as of July 2017 when ZHP knew this, correct?
MR. FOX: Objection to the form. Calls for speculation.
A. What we have in this document is a side statement in one sentence to this information. I don't know what's behind that, what the writer meant, particularly in Chinese -- I assume this was originally written in Chinese -- when he crafted this statement, what -- how deep his knowledge or understanding of that was or whether that was a speculative or off-the-cuff remark.
It's really very difficult to make any definitive conclusion from this about what the company actually knew and how many people knew it in 2017.
He's making an -- I guess you'd

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call it at minimum an allegation, or a suggestion maybe is a better way to put it, that this is the case. What the facts are behind that and how well-known they are, I have no idea.
BY MR. SLATER:
Q. With all due respect, that's not what I asked you, to give me every reason that you could come up with why someone might want to try to undercut the statement. That's not what I asked you. So let's go back to my question.
If, as stated in this document, ZHP knew that there was NDMA in the valsartan and it was a process impurity that was being created when the sodium nitrite quenching step occurred as part of the zinc chloride process, then everything you said ZHP was required to do in June of 2018 would be transferred back to July of 2017, or whenever earlier date they knew this, and all those things would have been required at that time, correct?
MR. FOX: Objection to the

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form. Lack of foundation, incomplete hypothetical, calls for speculation.
A. If they knew it, yes.
BY MR. SLATER:
Q. If they knew as of at least July 27th -- rephrase.
If ZHP knew at least as of July 27, 2017 that there was NDMA in the valsartan, and kept that secret and didn't tell any customers or any regulators until Novartis came to them and forced them to disclose this information in June of 2018, that would be a violation of the Food, Drug and Cosmetic Act, correct?
MR. FOX: Objection to form.
A. It would if it was offered for importation into the United States, yes.
BY MR. SLATER:
Q. We know that ZHP was selling its valsartan with NDMA in it right through until the recall occurred in June or July of 2018, right?
MR. FOX: Objection to the form.

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A. I haven't looked at their sales and distribution records. I know only that they had product on the market when they conducted the recall, or there wouldn't have been anything to recall.
MR. FOX: Adam, is there a reason why you're not appearing on any of these screens?
MR. SLATER: Is there a reason I'm not appearing? I'm looking right at myself.
MR. FOX: Okay.
MR. SLATER: I'm right below Mr. Chesney, where I belong.
THE WITNESS: I can see him.
MR. SLATER: He's sitting right on my -- he's got his feet right on my shoulders right now.
A. Actually you're at the bottom on my list, but I can see you.
MR. SLATER: I'm in here.
MR. FOX: Okay. I found you.
BY MR. SLATER:
Q. Okay. If, in fact, ZHP knew at

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least as of July 27, 2017 that there was NDMA in the valsartan and didn't tell its customers and didn't tell any regulatory authorities and just continued to sell the product, that would be a very serious violation of the Food, Drug and Cosmetic Act, correct?

MR. FOX: Objection to form. Argumentative, lacks foundation.

A. It would be of great concern if indeed that's true, but I don't know that it is.

BY MR. SLATER:

Q. In terms of your ability to form an opinion in this case, this is the type of information you would have expected to have been provided when you were provided materials by counsel, correct?

MR. FOX: Objection to the form.

A. If I had been provided this information, it would have raised certain questions in my mind. I would have referred those to scientific subject matter experts,

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but I would have taken note of it.

BY MR. SLATER:

Q. Let's go down a little further in this e-mail.

After the pictures of the potential formation route of the nitrosamine impurity in the irbesartan, the second paragraph under that says, "If it is confirmed as the above speculated structure, then its toxicity will be very strong, and there will be an extremely high GMP risk. This is a common problem in the production and synthesis of sartan APIs. It is recommended to improve other quenching processes (such as NaClO) along with the optimization of the valsartan sodium azide quenching process."

Do you see that?

A. I do.

Q. So this provides further information about the depth of understanding by ZHP as of July 2017, because this shows that they knew that this is a common problem in the production and synthesis of sartan

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APIs. That's additional important information, right?

MR. FOX: Objection to the form.

A. It also characterizes the findings up above as not confirmed and speculative.

BY MR. SLATER:

Q. The speculated structure is talking about what was being seen in the irbesartan, which was something they were working on to try to work on that process to manufacture it. They're not speculating about there being NDMA in valsartan; that's not stated as speculative at all, correct?

MR. FOX: Objection to form. The document speaks for itself.

MR. SLATER: Counsel, you have to stop, with all due respect, making a document speaks for itself objection. I would appreciate it if it would stop. I know you're new to this litigation, but the Special Master has instructed that that

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objection should not be made.

You don't have to take my word for it, I'm just trying to help.

BY MR. SLATER:

Q. Can you answer the question, please?

A. I'm just taking a minute to read it here.

(Witness reviewing document.)

A. I'm having trouble from these isolated paragraphs here making a link back to valsartan, frankly. I hear what you're saying, but I'm not able to get there based on what it says right here.

Q. I'll ask you a different question then.

You see the sentence that says, "This is a common problem in the production and synthesis of sartan APIs"? Do you see that sentence?

A. I do.

Q. That's not phrased as something he's speculating about; that's being stated as fact in this e-mail. That's how it reads,

right?
A. Yes.
MR. FOX: Objection to the form.
BY MR. SLATER:
Q. Did you say yes?
A. Yes.
Q. And we know in retrospect that this was a common problem in the production and synthesis of sartan APIs, which is why ultimately it turned out that other manufacturing processes were implicated in irbesartan and losartan, that there were recalls of those drugs as well. That was ultimately learned, correct?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. And in fact, Dr. Lin makes the responsible recommendation to improve the other quenching processes along with the optimization of the valsartan sodium azide quenching process. That's the responsible thing to say when you realize that your

manufacturing process is creating a genotoxic impurity, in this case NDMA, correct?
MR. FOX: Objection to the form.
A. You're talking about the last paragraph here.
Okay. I'm sorry, but I was catching up with you by reading this in a little more depth, could you either repeat the question or have it read back to me, please?
BY MR. SLATER:
Q. Sure.
It was responsible for Dr. Lin to state, as he did, that he was recommending that they improve the other quenching processes such as NaCIO, along with the optimization of the valsartan sodium azide quenching process, because of the fact that, as he stated, this is a common problem in the production and synthesis of sartan APIs. That's a responsible recommendation, right?
A. Yes, it is.
Q. In the last paragraph he

states, "I've also attached a patent of a 2013 sodium azide NaCIO quenching method by Zhejiang Second Pharma Co., Limited. They proposed that the use of NaNO2 quenching will result in the formation of N-NO impurities," which is N-nitroso impurities. "At the same time, they used ZHP's crude Valsartan in their LC-MS test" -- that would be liquid chromatography-mass spectrometry -- "and detected this impurity. This indicates that other companies have paid attention to the quality problem very early on. So leaders please pay attention to this issue."
Do you see that paragraph I just read?
A. Yes.
Q. Dr. Lin's statement to these other executives -- rephrase.
Dr. Lin's statement that other companies are aware of this quality problem, and giving an example going back to 2013, that's significant, isn't it?
MR. FOX: Objection to form.
A. It's my understanding that at

that point in time other companies had not conducted recalls or taken any market action with respect to the issue, so it sounds to me like it was something the industry was in the process of coming to an understanding of at that time.
BY MR. SLATER:
Q. Most important -- rephrase.
At the very end he says, "So leaders please pay attention to this issue." That is a very responsible thing to say in this e-mail, alerting the others that receive this e-mail of this situation with the creation of NDMA and the fact that it's a common problem in the production and synthesis of sartan APIs. It's responsible for him to tell the leaders in his company to take note of this situation, right?
A. Yes.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. And in fact, the leaders of the company, right up to the highest executive, would have the ultimate responsibility for

this quality problem, right?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. And you've actually written on that subject and published on that subject, correct?
A. Yes.
Q. You would agree with me as a matter of GMP that the information in this e-mail could not be ignored; it needed to be aggressively evaluated by the so-called, quote-unquote, leaders as soon as it was brought to their attention, right?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. And we know in retrospect that what Dr. Lin said about the valsartan quenching creating the NDMA and this being a common problem in the production and synthesis of sartan APIs, we know in retrospect he was 100 percent correct about those statements. You've seen that in the

materials you've reviewed for this case, right?
MR. FOX: Objection to form. Argumentative.
A. Ultimately that information was developed, yes.
BY MR. SLATER:
Q. Are you stunned to see this e-mail, and to see that this information was being circulated within ZHP as of July 2017? Because you said it's the first time you've become aware of that.
MR. FOX: Objection to form.
BY MR. SLATER:
Q. Are you stunned, shocked, surprised? What word would you put on it?
A. I wouldn't say stunned. It sounds to me like an appropriate notification based on some information that is outlined in the e-mail.
It's a few months before -- actually about -- let's see here, about 10 or 11 months before the recall, and these things are -- complex scientific issues like this

don't get resolved overnight.
I don't know what was done about this, whether this was a triggering point for further work that culminated in the notification to FDA and the recall, or what.
But it certainly is responsible for Dr. Lin to have made this notification, and it looks like he made it to the right people.
Q. We know, again in retrospect, that what Dr. Lin said is accurate, and we know that he must have had a way to know it because -- well, rephrase.
You're certainly not taking the position that he just came up with this out
[redacted]
MR. FOX: Objection.
MR. SLATER: Chris, let's go to

the article in the Quality Management Essentials publication that I just mentioned a moment ago indirectly, please.
And I'm not sure what exhibit number would this be for the record, if anybody knows.
MR. GEDDIS: That would be Exhibit 5.
(Whereupon, Chesney Exhibit Number 11 was marked for identification.)
MR. FOX: Which exhibit is this on the screen?
MR. SLATER: I think I was just told Exhibit 5.
MR. FOX: So this has not been used before.
MR. SLATER: This has not been used before.
BY MR. SLATER:
Q. And you recognize this publication, Quality Management Essentials, Expert Advice on Building a Compliant System?

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You recognize this publication from 2018, correct?
A. I don't recognize the artwork, but I recognize the title, yes.
Q. And if we go to the third page, the Table of Contents, we can see that you actually wrote an article that was included in this publication titled Executive Responsibility for Quality, correct?
A. Yes, that's correct.
Q. Let's go to your article which comes right after that. And this is titled -- rephrase.
Your article is titled Executive Responsibility for Quality, and I want to go to the section titled Importance of Quality just below that.
MR. SLATER: Chris, could you make it a little bigger, please?
Perfect.
A. That's fine.
Q. This says, "Importance of Quality.
"Executive commitment to

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quality in the pharmaceutical industry is critical, not only to ensure continuing profitability of the company, but also for the safety and well-being of patients and to meet the needs of healthcare providers who prescribe and use pharmaceutical products every day."
That's what you wrote, correct?
A. Yes.
Q. The primary concern has to always be the safety and well-being of patients, right?
A. Yes.
Q. It would never be acceptable for ZHP or any other company to place profits over safety, right?
MR. FOX: Objection to form.
A. I agree with that.
BY MR. SLATER:
Q. For example, if it turned out that ZHP was making so much money with the zinc chloride process to manufacture valsartan API that they chose to keep secret from its customers and the regulatory

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authorities that they knew there was NDMA in the valsartan because they were so enamored with the profits they were making and put that ahead of the safety of people using those pills, that would be reprehensible, right?
MR. FOX: Objection to the form. Argumentative, no foundation, beyond the scope of his expertise.
A. It would be of great concern, yes.
BY MR. SLATER:
Q. It would be reprehensible, right?
MR. FOX: Objection. Same objection.
A. That's a value judgment word. I prefer more precise terminology. But it would not be a good thing.
BY MR. SLATER:
Q. Going down a little further to the fourth full paragraph under Importance of Quality, there's a paragraph that says, "For these reasons, quality assurance (QA) and GMP

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compliance may be viewed differently in the pharmaceutical industry than in those industries where a reputation for high quality drives sales. Quality assurance may be viewed as a 'cost of doing business' or an internal 'police department' issuing directives that delay or prevent product release. That viewpoint can result in a low priority being assigned to quality operations and resourcing, which can lead in turn to quality problems, regulatory difficulties, unnecessary expense, adverse publicity, lawsuits and investor disappointment. All these consequences are preventable if executive managers understand the importance of the quality assurance function and treat it as a critical business operation just like other critical areas, such as strategic planning, financial management and others."
That's what you wrote because you believed it to be true, correct?
A. Yes, sir.
Q. Let's go now to the next page. There's a heading that says Regulatory

Considerations. And you wrote, "In addition to the business benefits, health regulatory agencies around the world both require and expect top management to support a strong quality assurance function for their companies."

Top management would include, for example, the chairman of ZHP, Mr. Baohua Chen; he would fall within the context of top management, right?

A. Yes.

MR. FOX: Objection.

I'm sorry, Adam, I didn't hear the name that you mentioned.

MR. SLATER: I said Baohua Chen. Mr. Baohua Chen.

BY MR. SLATER:

Q. You then go through, after introducing this section, a couple of cases from the US Supreme Court that addressed the executive responsibility for certain regulatory violations, correct?

A. Yes.

Q. The first case you talk about

is US versus Dotterweich where you say that "Mr. Dotterweich's company, Buffalo Pharmacal, was inspected by the FDA, resulting in direct adulteration and misbranding findings. The FDA criminally prosecuted Mr. Dotterweich and the company, charging that as president, he was ultimately responsible for the company's actions and therefore should be found guilty of violating the law."

And you put that in the article because you found that to be a significant case and a significant cautionary tale, correct?

A. Yes.

Q. You said, "Following a District Court case and subsequent appeal, the Supreme Court ruled on his case and concluded that as president, he could be held responsible for the acts of the corporation even though he did not know of the violations and did not intend for them to occur. This has become known in the US as the Doctrine of Strict Liability, or 'Responsible Corporate Officer'

doctrine. It applies to those who, in the words of the Court, '...stand in a responsible relationship to the acts of the corporation.'"

And again, you stated this because you're cautioning the executives in pharmaceutical companies to take their quality obligations very seriously, right?

A. Yes.

Q. You then talk about the Park case, US v. Park, and you say in part, "Like Mr. Dotterweich, Mr. Park defended himself by claiming that he was not involved in the conduct that violated the law and that he had delegated authority to 'dependable subordinates' he trusted to do the right thing."

And a little further down you actually quote from the majority opinion from the Supreme Court stating, "The Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will ensure that violations will not

occur.

"The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding and even onerous, but they are no more stringent than the public has the right to expect. We are satisfied that the Act imposes the highest standard of care and permits conviction of responsible corporate officials, who in light of this standard of care, have the power to prevent or correct violations."

And you quoted that language because you felt it to be, again, not only a cautionary tale, but right on point to get the attention of executives, correct?

A. That's right.

Q. When you talk about demanding and even onerous obligations and the highest standard of care, those statements would apply to ZHP, too, right, and their executives, correct?

MR. FOX: Objection to form. Calls for conclusion.

A. In my opinion they apply to anyone in the FDA-regulated industries.
BY MR. SLATER:
Q. Looking now on page 5, if you could. Towards the bottom, you provide at the bottom, you say, "some general suggestions that apply to all companies in this industry, regardless of size or complexity."
And number 1, you say, "Executive managers must recognize the criticality of a strong quality assurance organization and quality system to patient safety and to the company's business success."
And that's an important foundational point, right, that QA has to be prioritized? Right?
A. Yes.
Q. Looking at number 2, "Quality management must be seen as similar to other critical business management activities executives participate in, such as strategic planning, budget management, succession

planning and other areas."
And then number 3, you say, "Executive management teams must support their QA organization with authority and resources that are equal to the responsibility they have."
And then you say a little further down that the structures within the company "must assure that the quality unit can make decisions without undue influence from other organizational components and avoid conflict of interest."
Again, these are all what you believe to be very important points for any responsible company to follow, correct?
A. Yes, that's correct.
Q. Number 4, you wrote, "Executive management must establish a strong quality policy that makes it clear the company is committed to consistently producing high-quality products that perform clinically as intended. Day-to-day statements and actions of top level executives must demonstrate that this commitment is real, not

just words on paper."
I wanted to ask you about the "words on paper" part, because that jumped out to me when I read this.
That's an important point to you, that it's not enough just to put these policies in writing, but you actually have to be committed to following through with them and taking these obligations seriously, right?
MR. FOX: Objection to form.
A. Yes.
BY MR. SLATER:
Q. Number 5, you say, "As with other management responsibilities, executive teams must be kept aware of the performance of the quality system and of any emerging problems that are being dealt with."
MR. FOX: Is that a question?
BY MR. SLATER:
Q. That's another important point that you felt needed to be communicated to executive management in pharmaceutical companies, correct?

A. Yes.
Q. And I think overall what I'm hearing here is that the top level management has to essentially make very clear to everyone in the company that quality is very important, safety is very important, and it should never be minimized and never be put aside for considerations of profit, correct?
MR. FOX: Objection to form.
A. Yes, correct.
BY MR. SLATER:
Q. Did you read in the FDA documents where Jung Du told the FDA investigator that the zinc chloride process allowed them to increase their yield and lower their cost, and to thus dominate the world market for valsartan?
Did you see that statement?
A. Yes, I did.
Q. That's a concerning statement to you, isn't it?
MR. FOX: Objection to form.
Calls for speculation.
A. Well, it's a statement that's

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not unreasonable to make if there are benefits to -- you know, enhancing the process for those reasons, that's fine, as long as these other principles we've been discussing are given proper consideration. There's nothing wrong with improving a process, there's nothing wrong with being profitable for that matter, provided that these other principles are respected.

BY MR. SLATER:

Q. With regard to the e-mail I showed you from July of 2017, matched up against what Jung Du told the FDA investigator, does that cause you some concern about whether or not ZHP kept secret its knowledge that there was NDMA in their valsartan because they were making so much money?

MR. FOX: Objection. Calls for speculation.

A. I don't see any connection on the surface of it. I think that e-mail by itself certainly is the type of upward communication that I'm talking about here

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that should be made on a regular basis. But there are many questions about what was then done about it, how complete and accurate its foundation was and all that.

But that's exactly the sort of thing that should be -- questions that should be asked when someone like Dr. Lin raises that kind of an issue to upper management.

BY MR. SLATER:

Q. If a decision was made not to investigate in any detail this issue and not to disclose it in any reports or to anybody because of the profits that were being made with this valsartan API, that would be a very, very serious problem, right?

MR. FOX: Objection to form. Calls for speculation, argumentative.

A. I've certainly seen no evidence that that was the case. But if it was the case, then yes, it would be of concern.

BY MR. SLATER:

Q. Going now to the Summary at the -- one second actually.

Looking at the next section, it

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says, "Common Mistakes Executive Teams Make," number 3 you wrote, "Emphasizing production quotas and market demands to the extent that quality problems are overlooked or regarded as unimportant - worst case, deliberate coverup of known quality problems through falsification of records." I'm going to stop there.

When you say, "worst case, deliberate coverup of known quality problems through falsification of records," you're saying that would be as bad as it gets pretty much, right?

A. Yes.

Q. Are you aware that -- well, rephrase.

To the extent that ZHP knew there was NDMA in its valsartan as of July 2017 or earlier, yet continued to represent to customers and regulators and the world that what they were selling was valsartan of the expected quality and the expected purity and didn't disclose the NDMA deliberately, that would be as bad as it gets, right?

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MR. FOX: Objection to form.

BY MR. SLATER:

Q. If that happened, that's as bad as it gets, right?

MR. FOX: Objection to form. Lacks foundation, calls for speculation.

A. I don't see enough in the July 2017 e-mail to enable me to conclude with finality that the premise of your question is accurate.

There certainly are some concerns expressed there that are appropriate to express, they're being expressed to the right people. But full background and all the facts would have to be delved into with considerable effort in order to reach a conclusion that would have that much impact.

BY MR. SLATER:

Q. If the conclusion that I postulated were the facts, you would agree that that would be about as bad as it gets, right?

MR. FOX: Objection to the

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form. Calls for -- it's argumentative.

A. Once again, if after a complete investigation considered all the facts, if it was established and proven based on objective evidence that information existed that was known was deliberately covered up or anything was falsified, then that would be a very serious violation, yes.

BY MR. SLATER:

Q. Looking now at the Summary, you talked about the fact that there is a "growing consensus about the most critical quality management concepts." And you say, "First among those is that executive management teams are the key to a company's ability to successfully meet quality standards on a consistent basis. Doing so is critical to proper clinical performance of the products of this industry and therefore, ultimately, to global public health."

And you would apply those -- that point to ZHP? Those points would apply to ZHP, right?

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A. I'm sorry, Adam, can you just have that repeated? It got garbled.

Q. This would apply to ZHP, correct?

MR. FOX: I'll object to the form because I didn't hear it.

BY MR. SLATER:

Q. I read the -- I'll do it again.

You say in the Summary that certain -- rephrase.

You say in the Summary that there's a "growing consensus about the most critical quality management concepts. First among those is that executive management teams are the key to a company's ability to successfully meet quality standards on a consistent basis. Doing so is critical to proper clinical performance of the products of this industry and therefore, ultimately, to global public health."

And you would agree that within ZHP, the ultimate responsibility lies with the executive management team, correct?

MR. FOX: Objection to form.

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A. Yes, I would agree it applies to ZHP and everybody else in the industry.

BY MR. SLATER:

Q. Let's go to the last page, please. It's there already, sorry.

The last paragraph of this article says, "Prudent management teams recognize this and support their quality units both philosophically and materially, with strong policies backed up by consistent actions, authority and resources. Failure to do so may have both serious business consequences for the company and potentially even personal consequences for individual executives."

Again, that's a statement that you believe would hold true for ZHP and any company in this industry, right?

A. Yes, any company in this industry.

Q. Going back to the events of 2017, if ZHP knew that there was NDMA in its valsartan as of at least July 2017, yet continued to manufacture that valsartan with

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the zinc chloride process, didn't change anything, didn't tell anybody, every pill manufactured with that process would be adulterated, right?

MR. FOX: Objection to form.

A. I'm sorry, I'm giving some thought to the way you phrased that, not the concept, but just the phraseology.

If there was proven evidence that the process was contributing NDMA at harmful levels, and they allowed that to continue and continued to sell the product, and particularly if there was any deliberate effort to conceal that, then yes, that would be very serious.

MR. SLATER: If you guys need a break, this would be a good point because I'm going to shift to something else. But if you don't need a break, I can do it.

MR. FOX: Let's take a break, Adam, because I have to take care of something else for a few minutes, too.

A. I need a couple minutes.

How much time do you want to take here?
MR. FOX: About 3:15?
THE WITNESS: Okay. What time is it now?
MR. SLATER: That's fine.
THE WITNESS: Okay. 3:15 is good.
MR. SLATER: Thank you.
THE VIDEOGRAPHER: The time is 2:54 p.m. We are off the record.
(Whereupon, a recess was taken.)
THE VIDEOGRAPHER: The time is 3:23 p.m. We are back on the record.
BY MR. SLATER:
Q. Mr. Chesney, have you seen any indication in anything you've seen that ZHP has ever notified the FDA about the contents of the July 2017 e-mail we discussed earlier?
MR. FOX: Objection to form.
A. The existence of the e-mail itself?
///

BY MR. SLATER:
Q. Well, the contents we've been talking about, including that there was NDMA in valsartan --
A. Well, the --
Q. -- how it was being created at the quenching of the sodium azide, the sodium nitrite, and that it was a common problem with sartan APIs?
MR. FOX: Objection to form. Argumentative, lacks foundation.
A. There was extensive back and forth with the FDA. ZHP submitted a tremendous amount of scientific data. FDA asked questions, ZHP responded. I've seen a lot of that. Some of it may have contained information that was foundational to that July of '17 e-mail or may not.
But the existence of the e-mail itself, I haven't seen reference. It's just the information that it refers to may have been wrapped up and included in some other discussions that were held with the FDA.
///

BY MR. SLATER:
Q. I understand you're saying maybe it was, but nothing you can recall seeing as you sit here now, right?
A. No, and nothing specific about that particular e-mail.
Q. Did you see any indication in anything you reviewed where ZHP suggested to the FDA or anybody else that it was known internally that there was NDMA in valsartan, and that this was caused by the quenching of the sodium azide with the sodium nitrite, that that was known before June of 2018? Have you seen anything indicating they ever told that to anybody?
MR. FOX: Objection to form. Lacks foundation, argumentative.
A. Again, I would have to look at the correspondence back and forth to refresh my memory as to what happened when and what they told the FDA about the timeline. But as I sit here, I can't recall anything.
BY MR. SLATER:
Q. I'm going to jump through a

couple of things with you.
One of the things I noticed in your report was that you said that the time period that you focused on was August 2013 to October 2019, other than, I think, one complaint from 2010 that you found on the FDA website.
Do I understand that correctly?
A. Not exactly. That wasn't a complaint on the FDA website. It was a record of a prior inspection. And there was -- you know, that was not within that bracketed time period.
But the majority of the documents I reviewed were within that bracketed time period.
Q. Do you have any understanding -- rephrase.
Why would the time period you were looking at beginning 2013 when the manufacturing process change was vetted and evaluated in 2011?
A. Well, the primary remit I was given was to opine on what the record showed

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for ZHP's GMP compliance status, and most of the records that I was supplied, the vast majority of them, began in 2013 and ran up until that latter date.

I was able to extract from the FDA website a couple earlier references, and at least one later one when the warning letter was closed out formally by the agency. But most of it was in that time period.

[redacted]

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[redacted]

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[redacted]

BY MR. SLATER:

Q. You talked a lot about the

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events after the 483s, the warning letter, and the establishment inspection report. You talked a lot about what happened after that, and talked about the fact that, well, eventually they got a closeout letter, and eventually they got the import alert over three years later. You talked about that in your report, right?

A. Yes.

Q. The point is that there were violations the FDA found, and then those violations had to be remedied on a going forward basis. And that's what you're talking about would happen on a going forward basis; you're not saying that these violations didn't exist before, right?

MR. FOX: Objection to the form. Assumes facts not established.

A. One of the contributing factors I'm sure in that three-year delay you alluded to was the COVID pandemic. FDA's action in closing out the warning letter probably could have been done much more promptly had it not been for that. That slowed down a lot of

things at the FDA. In fact, they're still dealing with the backlog caused by that, so that may have been one contributing factor.

You know, that whole process of bringing the warning letter to the fore, issuing that, taking the import alert action and clearing all those things up, those things happen very slowly in normal times, and with the intervention of the pandemic, I'm sure it slowed it even further.

BY MR. SLATER:

Q. Aside from the timing of how long it took, the fact of the matter is that the FDA found some violations, and then ZHP had to take steps to remedy those situations before it could get a closeout letter and get off the import alert, correct?

A. With respect to the warning letter, the FDA's formal position is that that's an advisory action, not a final agency determination of noncompliance.

And what they characterized those items in the warning letter as internally is observations of regulatory

significance. They don't term them to be violations because they've not truly been adjudicated at that point in time.

Q. I did some reading, and my understanding is that the warning letter is actually a very serious document because the assumption is it's going to get the attention of the company and get the company to fix the situation so that the FDA doesn't have to escalate to direct legal action in court.

A. That's correct. I didn't say it wasn't a serious event. It is a serious event. It's just that the agency's official position is that it is an advisory notification intended to stimulate, bring about voluntary corrective action, and also to serve as prior notice in the event they do have to escalate, then they can make showing that they gave the company the opportunity to correct things voluntarily.

Q. For the companies, for example, that you consult on -- rephrase.

For the companies you consult with, when they get a warning letter, you

take that very seriously and you make it clear to those companies to take them very seriously, right?

A. Without question, yes.

Q. I mean, a warning letter is not something that happens every day, and it's a big event in a company's lifecycle that they have to really focus on and deal with very, very seriously, right?

A. A warning letter is not something that happens every day to a company, but it's something that happens every day at the FDA. They're not uncommon events.

Q. I guess really, I think we've talked about through, but I got the sense that maybe there was a suggestion that a warning letter, because it's not a binding legal action, that it somehow has some kind of minimal significance. That's not what you're saying?

A. Oh, no, not at all. I'm sorry if I conveyed that impression. That was not what I intended.

Q. We're going to digress into something really random right now, which is to clear something up actually.

MR. SLATER: Chris, do you have the Exhibit B addendum to the reliance list? I just realized I never marked it as an exhibit. The addendum we got the other day.

MR. FOX: What is this?

MR. SLATER: I'm sorry, what?

MR. FOX: Okay.

MR. SLATER: I think, Chris, this is Exhibit 12 now, right?

MR. GEDDIS: Yes.

MR. SLATER: Okay. Just for everybody to know, we had talked about what exhibit numbers there were. The exhibits have been getting marked sequentially in the deposition. Even though a lot of them had numbers from prior depositions, we've marked them for purposes of this deposition as well so that we know which ones were actually used here, so they're marked

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specific to this deposition as well.
So this is Exhibit 12.
(Whereupon, Chesney Exhibit Number 12 was marked for identification.)
BY MR. SLATER:
Q. Mr. Chesney, we were provided this the other day, a list of additional references as an addendum to Exhibit B.
Are these materials that you have read?
A. Not in their entirety. At the onset of this engagement I accessed a number of things that were publicly available just to get some context and bring myself a little bit more up to speed on what was going on with the nitrosamine issue.
So these are things that I've pulled from various sources, took a look at, took what I could get from them, more for orientation and contextual purposes and not for specific reliance during the formation of the opinion I submitted in this matter.
Q. Were these materials that you

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had available -- rephrase.
Are these materials that you had at least looked at before you signed your report --
A. Yes.
Q. -- or things you looked at after?
A. Yes. I looked at them, most of them, at the very beginning of this engagement back, whatever it was, in June of 2021 when I first started doing the work, just to get a sense of the issues and what some of the guidance documents were that FDA and others have come out with on this topic.
Q. Okay. In terms of the methodology that you followed here -- well, rephrase.
In terms of your normal methodology, if I understood before, normally what you would do when you're evaluating the GMP compliance status for a particular manufacturer would be to evaluate the relevant documents that are available, the internal standard operating procedures that

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would apply, and I think also you said you would do this in a multidisciplinary way where you would rely on subject matter experts with regard to the scientific questions to give input that you could then rely on to give an ultimate opinion.
I don't mean to oversimplify, so if you want to tell me a little more you can, but that was generally my understanding of your methodology for evaluating GMP compliance status.
A. Well, let me expand that thought a little bit, if you may.
If I'm doing this for a client in the sense of either an audit or any other type of consultative activity, then my approach would be more or less the way you mentioned, looking at standard operating procedures perhaps, looking at the actual facility, watching operations, looking at investigations they've done, and things of that sort.
For this engagement what I was provided was a lot of FDA documentation,

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communication from the company and so on.
So the way I approached it was first to try to get myself a little bit of a briefing on the general issues. I had read, as I mentioned before, about the NDMA issues, I thought it would help if I understood a little more depth about what was going on here, so I accessed some of these documents for that purpose. It was just for orientation.
Then when I got into the documents themselves, I looked at them through the same eyes I would have looked at when I was reviewing identical kinds of documents at the FDA, which I did for many, many years. And I relied to a large extent on FDA's published methodology for doing the same thing, which appears for the most part in their compliance program guidance manual which gives -- all of those programs in part Roman Numeral V, gives instructions to reviewers for what kinds of observations should be considered significant and what regulatory pathways are appropriate in

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different fact situations.

So I apply the FDA's own published methodology to determine whether the establishment inspection reports were appropriately classified by the agency based on their own criteria.

I also read the establishment inspection reports to determine if the investigators followed the compliance program requirements, collected the correct information, whether their statements are objective or conclusionary, whether they're substantiated with appended evidence. I have a number of factors that I apply that are really the same that I applied when I was reviewing those reports for many years in the FDA.

Q. So ultimately, if I understand correctly, when you were evaluating the GMP compliance status, you were doing it through the prism of the back and forth with the FDA and the FDA documents for the most part?

A. Largely, yes.

Q. And I think that with regard to

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the -- rephrase.

We've talked quite a bit about this, so I'm not going to go back into it in any detail, but with regard to scientific issues, that's an area where you've told us you would defer. And since you don't have that at this point you didn't offer opinions in your report as to whether or not there were GMP violations because you would need that input before you could form that opinion, correct?

A. Yes, that's correct. And furthermore, the law firm I started working with on this matter, we discussed that angle, and I told him what my limitations were. When we entered into my retention in this matter, I told him there were certain scientific issues that were going to come up that I would not be the best expert to address.

And they understood that, said that they had other people that they were working with that could provide that perspective, and not for me to be concerned

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about that, but just to indicate in my report any areas where I was, in fact, deferring to others. And I attempted to do that as I wrote the report. I think you've seen that.

Q. Got it.

A. Some other documents I relied upon that are referenced in part in the report include the FDA regulatory procedures manual, and certain other publicly available guidance documents that the agency has out there.

Q. And at this point we've also talked about some documents and some information you hadn't seen yet. Ultimately if you were to form an opinion, you would want to be able to be assured that you had the relevant documents in doing so, right?

A. Well, yes. But I believed I had sufficient information there to make general conclusions and form an opinion as to what the overall compliance status of the facility was.

Q. The overall compliance status as we talked about from 2013 to 2019,

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correct?

A. That was the major focus, yes, with some excursion back to as early as 2010.

Q. That excursion was to one investigation, or one inspection?

A. Yes, that's right. I think there was also -- well, no, I guess that would be within the time frame that I bracketed.

I think there was another inspection that -- in one of the establishment inspection reports, the FDA person made a statement that the prior inspection was of a certain date, and when I looked at the record, the public record on the FDA data dashboard, there was an inspection that they weren't aware of that they omitted from their text.

So there were a few little gaps like that.

Q. And overall, for you to be able to form an opinion as to whether GMP was met or not, if you were to do your full-blown methodology, you would want to -- you would

need to have the full relevant documents. And as you've seen today, you didn't necessarily have all those, the necessary testimony to be able to understand what would actually happen, you would need all that in order to form such an opinion, correct?

MR. FOX: Object to the form.

A. If there are material omissions, or if there were material omissions in what I was given to review, I was certainly unaware of that at the time.

And, you know, of course, if things like that come to light, I become aware of them, it's something I would want to see.

BY MR. SLATER:

Q. And you would need to see to be able to form an opinion ultimately if it exists, right?

MR. FOX: Objection to form.

A. Yes. But I don't generally speculate that there's something that is not being provided to me. Unless I'm trying to reach a conclusion and don't have adequate

information, I would not presume to ask a question such as, Is there anything you're deliberately withholding from me for any reason, because I wouldn't assume that to be the case.

BY MR. SLATER:

Q. You assumed you were provided all of the relevant documents, correct?

MR. FOX: Objection to form.

A. I did. And that assumption was bolstered to some extent by my comfort that I had quite a bit of information from which to draw an appropriate conclusion.

MR. SLATER: Why don't we go off the record for five minutes. I may be done, I just want to double-check my notes and then we can -- then I can hand it off to Mr. Fox if he has questions too.

THE VIDEOGRAPHER: The time is 3:44 p.m. We are off the record.

(Whereupon, a recess was taken.)

THE VIDEOGRAPHER: The time is

3:47 p.m. We are back on the record.

MR. SLATER: Mr. Chesney, thank you. I don't have any other questions for you, unless counsel questions you, in which case I may follow up on his questioning.

MR. FOX: I have a few questions, Mr. Chesney.

EXAMINATION

BY MR. FOX:

Q. Do you recall that counsel showed you an e-mail from July 27, 2017, ZHP 296?

A. Yes.

Q. And does that e-mail involve scientific information of the type that you're not an expert to decipher?

A. Yes.

MR. SLATER: Objection. You can answer.

BY MR. FOX:

Q. I'm sorry, did you answer?

A. Yes, it does.

Q. Now, according to --

plaintiffs' counsel indicated that there had been testimony taken on that document. Are you aware that there will be additional testimony about that document?

MR. SLATER: Objection. You can answer.

A. No, I wasn't aware of that.

BY MR. FOX:

Q. Have you spoken to the author of that document?

A. No, I have not.

Q. From the substance of the document that was shown to you and that you read, can you determine definitively what was going on in that document?

MR. SLATER: Objection. You can answer.

A. No. As I said when Mr. Slater asked the question earlier, there are some issues there that are being brought to the attention of upper management, and that seemed to me an appropriate thing to do. But I cannot independently judge fully the significance of the issues.

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BY MR. FOX:
Q. Based on your review, did that document indicate that NDMA was in valsartan API?
A. It alludes to that at one point. But there's -- you know, again, I can't determine how reliable that statement is or how well substantiated it is. Those are the kinds of questions the leadership team should be asking, and others. Once they get that notification, they should ask for a more complete briefing.
Q. Is it your normal practice to opine on company documents?
A. I'm sorry, Mr. Fox?
Q. Is it your normal practice to offer opinions on company documents?
A. Yes, some. If a client asks me to and it's within my expertise, yes.
Q. Okay. Was the document dated July 27, 2017 within your expertise?
A. No.
MR. SLATER: Objection.
You can answer.

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BY MR. FOX:
Q. You were asked questions earlier by plaintiffs' counsel about unknown peaks, correct?
A. Yes.
Q. Do you remember that testimony?
A. I remember the topic, yes.
Q. And did that topic come up in connection with an FDA inspection in May 15th to May 19th of 2017 --
MR. SLATER: Objection.
BY MR. FOX:
Q. -- at the Chuannan plant?
MR. SLATER: Objection. Lack of foundation.
A. I would have to either look at the inspection report or my report to see if there's any mention of that. My recollection is not precise on that.
BY MR. FOX:
Q. Okay. I'm going to ask you to turn to page 35 of your report.
A. Okay. Got it.
MR. SLATER: I'm sorry, what

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page did you say in the report?
MR. FOX: 35.
MR. SLATER: Give me one second. Okay.
BY MR. FOX:
Q. Do you see at the bottom of the paragraph it discusses an analysis of peaks?
A. Sorry, the bottom of the third paragraph, or...
Q. The bottom -- at the bottom of the page, the last six lines of the page.
A. Bottom of the page.
Yes, uh-huh, I have that.
Q. So is the issue of peaks a part of that inspection?
A. Apparently was, yes.
Q. And did ZHP respond to the issue raised with regard to the peaks?
A. Yes, they did.
Q. How did they respond to it?
A. Well, in at least one instance they said -- they characterized it as a, quote-unquote, "ghost peak with no product quality impact."

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Q. Do you understand why they referred to it as a ghost peak?
A. I have a general understanding. Again, I'm not an analytical chemist, I don't do these tests myself, but I have heard that reference made many, many times by pharmaceutical analysts, including those that were in my line of command at the FDA. So I have a general understanding of what it means.
Q. And you reported -- you stated in here that there was a report that in the entire year of 2016, there were nine occurrences out of nearly 95,000 batches.
Do you see that?
A. Yes.
Q. In looking at peaks, is the first step to analyze whether they're real or not?
A. Yes, usually it is.
Q. And is it a possibility that there could be aberrations in the test results?
MR. SLATER: Objection.

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You can answer.
A. It certainly is. That can come from a number of different sources, including dirty glassware, contaminated solutions, laboratory error. There a whole host of possible ways that these kinds of ghost peaks can appear, and that needs to be investigated and resolved as one of the possible sources.
BY MR. FOX:
Q. Did the FDA accept that nine occurrences out of nearly 95,000 batches was an aberration?
MR. SLATER: Objection.
You can answer.
A. I don't know what the FDA's opinion about that was.
BY MR. FOX:
Q. Well, does your report indicate that the FDA's action was consistent with the view that the agency accepted the scientific rationale offered by ZHP?
MR. SLATER: Objection.
You can answer.
A. Let me look and see what --

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just let me back up for a moment here, Mr. Fox.
Yes, this -- the classification of this inspection reflects that the FDA would have deemed the compliance status of the facility minimally acceptable. That's their official term for that. That generally means there are a few observations, they are minor and not of regulatory significance.
So yes, that's a fair conclusion that they concurred that this did not indicate anything serious.
BY MR. FOX:
Q. And did it indicate, in your opinion, that the facility at that time was operating in compliance with GMP?
MR. SLATER: Objection.
You can answer.
A. Well, I base my opinion on more than just this, but certainly this didn't cause me to hold an opinion that they were not in compliance with GMP.
BY MR. FOX:
Q. I believe your testimony is

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that you don't have the scientific background to make an independent judgment with regard to the scientific chemistry issues raised, but you're capable of understanding what the FDA's perception of that scientific evidence was?
A. Yes. My capabilities are sufficient that if a subject matter expert offers me a technical explanation, I can usually follow most of it.
And if I have questions of areas that I don't understand, then I ask further followup questions. Usually we can reach accord to where they can explain it adequately to my satisfaction, and I can understand what they're telling me.
So in other words, I have a modicum of understanding of these things, but I am not an independent subject matter expert.
Q. The fact that a company experiences ghost peaks that are viewed to be an aberration, can a company still be compliant with GMP?

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MR. SLATER: Objection.
You can answer.
A. Yes, they can. In fact, in my personal experience, this happens frequently in pharmaceutical testing laboratories.
And my last job in the FDA when I was district director for San Francisco, I had a staff of approximately 50 analysts, of whom 10 or 15 were pharmaceutical chemists. And I know that even in the lab that was in my line of command and control, this issue was not infrequent.
So the FDA itself runs into ghost peaks, they resolve them ad hoc as they come up.
BY MR. FOX:
Q. And during your -- counsel's questioning of you, he showed you a couple sentences here and there in a couple of scientific publications, correct?
A. Yes.
MR. SLATER: Objection.
You can answer.
///

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BY MR. FOX:
Q. Is it outside of your scientific expertise, or lack thereof, to be able to make judgments concerning what was known in the scientific literature and the quality of that knowledge, given the sentences that plaintiffs' counsel showed you today?
MR. SLATER: Objection for multiple reasons, including it's argumentative.
You can answer.
A. I can't evaluate the technical sufficiency of those articles. There are some portions of it that I frankly don't even independently understand, although I might understand a good deal of it.
BY MR. FOX:
Q. Given the fact that you told counsel who retained you of your limited expertise when it comes to scientific issues, does it surprise you that you would not be provided all of the scientific data that may be involved in this case?

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MR. SLATER: Objection.
You can answer.
A. No, it doesn't surprise me, because one of the things -- this was one of the concerns I expressed is, Please don't expect me to be able to opine on the scientific questions. When they come up, I will have to say that I need to defer to people with appropriate expertise, and I was informed that those people would be retained separately and would take those issues up as they arose.
BY MR. FOX:
Q. In connection with the e-mail of July 27, 2017 that were shown you, ZHP 296, would you defer to other people for the correct interpretation of that document?
A. Yes, I would.
MR. SLATER: Objection.
You can answer.
A. Yes, I would.
BY MR. FOX:
Q. Earlier in the day plaintiffs' counsel asked you about the 2011 risk assessment.
A. Yes.
Q. And that was conducted in connection with the change in the manufacturing process?
A. Yes.
Q. Am I correct that you testified that you assumed that nitrosamines was a part of that risk assessment in 2011?
A. I don't think I understood the question if I said that. I was -- what I had in mind was the risk assessment that was done in four stages in 2018 and reported out in the response to the warning letter. That's really what I thought we were talking about, and I may have become a little confused as to the timing.
Q. Okay. So you never -- you never made the assumption that nitrosamines was part of 2011 risk assessment, did you?
MR. SLATER: Objection.
You can answer.
A. No, I did not.
///

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BY MR. FOX:
Q. Is there any reason why you would not make that assumption with regard to the 2011 risk assessment?
MR. SLATER: Objection.
You can answer.
A. The totality of the information that I had before me suggested that the industry at large was not really aware of this problem, nor had they developed robust tests to look for it until much later than that.
This appeared in the two public communications on that topic from the FDA; one I believe in the latter part of 2018, and one in January, I think it was, of 2019 where they repeatedly stated that there was not an awareness of this problem in the industry nor by regulators on a worldwide basis.
So based upon that, I would not have assumed that there was knowledge at ZHP or anywhere else in 2011.
Q. So you're aware of statements by the FDA that indicated that it was not

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part of GMP to look for nitrosamines in this process in 2018?
MR. SLATER: Objection.
A. Yes, I'm aware of those statements. And in those statements, the FDA said it really wasn't feasible for them to even look for that or evaluate it during inspections because there wouldn't be any records that they would be able to review that would reflect that type of analysis had taken place.
BY MR. FOX:
Q. Are you aware of the FDA ever stating that they were still not sure of the root cause of the NDMA impurity in the valsartan API?
MR. SLATER: Objection.
You can answer.
A. There's a statement that's still being worked on, I believe, in the 2019 pronouncement. The specifics escape me. I'm not looking at it right at the moment. But they did make a statement to that effect. I believe it was 2019 January statement.

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MR. FOX: Why don't we put up the -- why don't I put up a document here. Can we go off the record for a second until I get the technology down?
THE VIDEOGRAPHER: The time is 4:02 p.m. We are off the record.
(Off the record.)
THE VIDEOGRAPHER: The time is 4:04 p.m. We are back on the record.
(Whereupon, Chesney Exhibit Number Defendant 1, was marked for identification.)
BY MR. FOX:
Q. Mr. Chesney, I'm showing you a document of an FDA public statement made on January 25, 2019.
Do you see that?
A. Yes.
Q. And this is reference 91 in your report?
A. I'm not looking at the reference numbering list, but give me a moment, I will.

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Yes, that's it.
Q. And if I bring you down to the last paragraph of this page, and I'll just read it to you, it says, "Today, we want to provide an update on this ongoing investigation and outline the steps we've taken to identify the root causes of the nitrosamine impurities and to prevent a recurrence of this episode in the future."
Do you see that sentence?
A. I'm sorry, no, I don't. What I'm looking at starts "last summer."
Oh, there. Okay. "Today, we want to provide an update." Now I see it, yes.
Q. And so this was an update of an earlier statement that the FDA made in August of 2018?
A. Yes.
Q. And does this indicate to you that they're still identifying -- trying to identify the root causes of the nitrosamine impurities of valsartan?
MR. SLATER: Objection.

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A. Yes, it says it "continues to be an exhaustive effort led my a multidisciplinary team," which is the point I've been trying to make here today, that that's typically the way things are done at FDA. So I'm not surprised by that. A number of people in collaboration with global regulators.
And they go on to say, "While we're still investigating the root causes of the impurities, our ongoing effort has determined that the impurities may be generated when specific chemicals and reaction conditions are present."
So they're saying the investigation is ongoing, they have what sounds like a hypothesis in their sights, but it appears to be not yet concluded.
BY MR. FOX:
Q. If we go to the next page, do you see where it says in the beginning of the page, "To implement a risk assessment for any genotoxic impurity"?
A. I haven't found it yet. Sorry.

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Oh, there, "To implement a risk assessment." All right. I've got it.

Q. And doesn't that last sentence of the paragraph indicate that the FDA had now just uncovered the risk of nitrosamine impurities in the manufacturing steps involved in ARBs?

MR. SLATER: Objection.

You can answer.

A. I'm sorry, I was still reading the sentence, Mr. Fox. Could you repeat the question for me?

BY MR. FOX:

Q. Doesn't the FDA state in January 2019, quote, "Now that we've uncovered the risk of nitrosamine impurities in the manufacturing steps involved in ARBs, we'll incorporate the findings into ongoing policy development"?

A. Yes, they say exactly that.

Q. It says here -- do you see the sentence where it says, "Tests are selected based on assessments of what impurities may develop as a result of the manufacturing

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process. In other words, it generally needs to be recognized that there's a risk of an impurity occurring as a result of a manufacturing process to know the impurity should be tested for."

Do you see that?

A. Yes, I do.

Q. Can you read the next sentence into the record, "Our investigation"?

A. "Our investigation into ZHP's process identified that a change made to the manufacturing process likely led to this impurity, and that the impurity went undetected by global regulators, including the FDA, for a period of time."

Q. Can you read the next sentence?

A. Yes. Do you want me to read the whole paragraph?

Q. Sure, that would be fine.

A. "Before we undertook this analysis, neither regulators nor industry fully understood how NDMA or NDEA could form during this particular manufacturing process. This is troubling to us and we know it's

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troubling to the public. This concern is appropriate. Among other steps, we need to take actions that would prevent a similar situation from occurring. We are making important strides at understanding how these impurities occurred, mitigating the risk to patients and learning what steps need to be taken to prevent this from occurring again in the future."

Q. Does this indicate -- have implications for when GMP would have been implicated in connection with nitrosamines?

MR. SLATER: Objection.

You can answer.

A. I'm sorry? Was someone going to interject there?

MR. SLATER: I just objected to the form. You can answer.

THE WITNESS: Okay.

Yes, it indicates to me that certainly prior -- or as of the time of this transmittal to the public, there was enough understanding that companies should be pretty well aware.

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Prior to that time, the statement seems to say that there was not general recognition that this was a risk, and that, therefore, GMP would not require testing for something that no one had awareness could constitute a risk.

BY MR. FOX:

Q. If we go to the next page, can you read the first line of the paragraph beginning "During this time"?

A. Sure. "During this time, our scientists have developed and refined novel and sophisticated testing methods specifically designed to detect and quantify the NDMA and NDEA in all ARB medicines."

Q. And this is something that occurred between 2018 and 2019?

A. Yes, because this was not the case in the earlier 2018 public statement, but here we have it showing us January 25, 2019.

(Whereupon, Chesney Exhibit Number Defendant 2 was marked for

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identification.)
BY MR. FOX:
Q. I'm showing you now the earlier statement of the FDA that was referred to. Can you see that? Do I need to lower it?
A. You're going to need to shrink it a little bit, because the panel with all our pictures is overlapping.
There, now I've got it. That's fine right there.
Q. This is the FDA statement of August 30, 2018.
Do you see that?
A. Yes.
Q. And this describes the FDA's actions after learning about the impurity in the valsartan, correct?
A. Yes.
Q. If we go to the second page of it, maybe the third page, do you see the paragraph that says, "Based on information"?
A. Yes.
Q. Can you read that into the record, please?

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A. The whole paragraph?
Q. Yes, please.
A. Sure. "Based on information provided regarding ZHP's manufacturing processes, we believed (but did not have proof) that the impurity resulted from changes that ZHP made to the manufacturing process for its API. We needed to identify the root cause of the problem and evaluate ZHP's explanation. After assessing information about ZHP's manufacturing processes and the changes ZHP made over time, we identified how its processes could have led to the presence of NDMA in their API."
Q. Can you continue with the next paragraph?
A. "Specifically, a combination of conditions, which include certain chemicals, processing conditions and production steps, could lead to formation of the NDMA impurity. We believe that these risks are introduced through a specific sequence of steps in the manufacturing process, where certain chemical reactions are needed to form the active

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ingredient. Before we undertook this analysis, neither regulators nor industry fully understood how NDMA could form during this process."
Q. Let me just stop you there for a second.
A. Okay.
Q. Is that an important fact in connection with judging cGMP with regard to nitrosamines?
MR. SLATER: Objection.
You can answer.
A. Yes, it is, because it speaks to the feasibility of doing this and the general awareness in the industry of it.
BY MR. FOX:
Q. Given this extensive -- you would say the FDA's investigation was extensive, correct?
MR. SLATER: Objection.
You can answer.
A. I've only reviewed the records on ZHP, but their track record is pretty extensive there. I'm not sure what they did

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with the other manufacturers.
BY MR. FOX:
Q. Okay. But certainly this public statement is reflecting an extensive investigation that the FDA undertook of this matter?
A. Yes, it --
MR. SLATER: Objection. Form.
A. It infers that. It doesn't describe the full scope of the investigation with specifics, but it's implicit, yes.
BY MR. FOX:
Q. Now, if you continue with the paragraph that says "We are still."
A. "We are still not 100 percent sure that this is the root cause of the problem. Full understanding will require correlation of multiple test results from valsartan APIs made by different processes with the various process steps used by different manufacturers or at different times. We need to determine how NDMA can be formed and why it is not separated from the API during purification."

Q. Those statements by the FDA, is that important information for you in rendering an opinion with regard to compliance with cGMP by ZHP?
A. Yes, it is.
Q. Can you read the next paragraph, please?
A. "Once we understand the way or ways that the NDMA impurity can occur as a by-product of the manufacturing process, we will make sure" that these -- "make sure these conditions are evaluated in API synthetic processes so that, in the future, testing for this impurity would be required if there was a risk of NDMA formation."
Q. And again, is that an important factor in rendering an opinion with regard to ZHP's compliance with cGMP with regard to nitrosamines?
MR. SLATER: Objection.
You can answer.
A. Yes, because it lays out a two-pronged test to determine if something -- if this is GMP or not. One is, is there a

risk of NDMA formation; and two, if so, what is does the testing show.
BY MR. FOX:
Q. Okay. If you go down a little bit further, do you see the sentence that begins "We employ"?
A. Yes.
Q. Can you read that into the record, please?
A. "We employ robust teams of organic chemists, as part of our newly established Office of Pharmaceutical Quality, to review applications and referenced information to look for steps - and manufacturing changes - where these risks could be introduced."
Q. And if you look at the last sentence on the page, can you read that into the record?
A. "In other words, it needs to be recognized that the risk of an impurity can occur in order to know that it should be tested for."
Q. Is it fair to say that prior to

this date, the FDA did not understand there to be a risk of an impurity in this manufacturing process?
MR. SLATER: Objection.
You can answer.
A. It is. That's what the agency states in this public statement.
BY MR. FOX:
Q. Let's see. I lost my place.
Okay. If we go to the next page here, do you see -- can you read into the record the sentence beginning with the word "Because" in this top paragraph?
A. Yes. Do you want me to read that?
Q. Please.
A. Okay. "Because it was not anticipated that NDMA would occur at these levels in the manufacturing of the valsartan API, manufacturers would not have been testing for it. They would not have records that help identify this issue during an inspection. So this particular risk would not have been identified on an inspection.

As we develop a better understanding of the root cause of NDMA formation, and develop a way to detect NDMA in valsartan or other ARBs, we can ensure that appropriate testing is performed in the future."
Q. Again, is this an important fact in determining whether or not GMP was compliant in connection with nitrosamines in 2018?
A. Yes.
MR. SLATER: Objection.
You can answer.
A. Yes.
BY MR. FOX:
Q. And before 2018, correct?
A. Yes.
Q. And is it true that the FDA is again stating that they're still seeking to better understand the root cause of the formation of this impurity? Is that right?
MR. SLATER: Objection.
You can answer.
A. Yes.
///

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BY MR. FOX:
Q. And it's also saying in August of 2018 that they need to find better ways to detect it.
MR. SLATER: Objection.
You can answer.
A. Yes.
BY MR. FOX:
Q. Is it your testimony that the compliance record of ZHP was in accord with or even better than much of the industry during the period that you reviewed?
MR. SLATER: Objection.
You can answer.
A. Yes. But they had many inspections that led to no observations at all, and most others, while they might have had a small number of observations, they were classified by the agency as voluntary action indicated, which is a mid-level classification that does not reflect a serious state of noncompliance.
BY MR. FOX:
Q. Did the FDA ever determine that

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the nitrosamine or NDMA present in the valsartan was the result of a violation of GMP?
MR. SLATER: Objection.
You can answer.
A. I don't -- I've never seen them make that specific correlation. In the warning letter they raised certain concerns, but I don't believe they ever came right out and made that connection.
BY MR. FOX:
Q. So as far as you understand, the FDA never made a determination that the impurity existed in the valsartan as a result of a failure to comply with GMP?
MR. SLATER: Objection.
You can answer.
A. I never saw anything that connected those two issues directly.
BY MR. FOX:
Q. Are you aware of any GMP violation that would render all of the products of ZHP adulterated?
MR. SLATER: Objection.

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You can answer.
A. Well, hypothetically I suppose you could use your imagination and come up with something that would be so global in scope that it would cause that.
But usually when that is the case, and all the products at a given facility come under that kind of cloud, it's not just because of any one GMP deviation, it's because there are multiple ones of a systemic and repeated nature across all of what FDA calls product classes in that particular -- profile classes, pardon me, in that particular facility.
BY MR. FOX:
Q. And you have not seen that in connection with ZHP here, have you?
A. No.
MR. SLATER: Objection.
You can answer.
A. No, I haven't.
BY MR. FOX:
Q. And did the FDA ever make a final determination of a GMP violation by

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ZHP?
MR. SLATER: Objection.
You can answer.
A. I believe the import alert that they were placed on, along with many, many, many other companies, was primarily predicated upon GMP issues. But again, there was no specific linkage to the occurrence of NDMA.
BY MR. FOX:
Q. So was the alert due to the potential of an impurity being in the drug?
MR. SLATER: Objection.
You can answer.
A. The alert is very nonspecific. It gives a general statement with respect to GMP compliance, I believe it's one sentence, and then there's a list of dozens and dozens and dozens of companies that follow that are on the import alert for that reason. So it's very hard to tell anything specific from the import alert.
BY MR. FOX:
Q. And the language that you're

referring to, that's template language at the top of the document?

A. It is.

MR. SLATER: Objection.

You can answer.

A. It is.

And I might add that the standard that FDA applies by statute to bring an import alert action is one of an appearance of a violation, not even a preponderance of the evidence, let alone beyond a reasonable doubt. The standard is very, very low.

And I'm getting that directly out of the Food, Drug and Cosmetic Act Section 801. If it appears to be in violation, that's sufficient to take an import alert action. It's a very low standard.

BY MR. FOX:

Q. Did the FDA ever make a finding that the NDMA contamination was due to a cGMP violation?

A. I've never seen them connect --

MR. SLATER: Objection.

You can answer.

A. I've never seen them connect those two issues directly in anything they've said in writing.

BY MR. FOX:

Q. With regard to ZHP?

A. With regard to ZHP.

MR. FOX: I think that's it for me, Adam.

MR. SLATER: I'm going to continue now, Mr. Chesney.

FURTHER EXAMINATION

BY MR. SLATER:

Q. Did you read the deviation investigation reports that ZHP created and submitted to the FDA?

A. You know, I read an awful lot of information. And to answer your question whether I did or did not look at those, I would have to go back and look at them again just to be sure. But I believe that I did.

Q. I didn't see any discussion of them in your report.

A. I read a lot of their investigation information, particularly what was in the response to the 483 of the 2018 inspection which raised most of these issues, and also the warning letter that followed. There was a tremendous amount of highly detailed information. One of those transmittals alone was 230 pages.

So to the extent that constituted in whole or in part the deviation investigations, I can't say from memory. It was very extensive.

Q. All right. Well, I didn't ask you about all that stuff.

I asked you if you saw the deviation investigation reports, and did you talk about them in your report. I don't see any discussion of them at all in your report. Is there something in the report I've overlooked?

A. Well, I doubt that there's anything in the report you've overlooked.

What I'm saying is what constituted a deviation investigation report

may well have been the information in the warning letter response and other documents that I reviewed. They also included a number of attachments.

Q. Are you just speculating as you go right now?

A. No. I'm trying to say that I can't answer your question with definity because I don't know what you mean when you say "a deviation investigation," and I'm not sure whether it was included or not included in any of the materials that I did review.

MR. SLATER: Okay. Chris, let's go to exhibit -- let's take down whatever this is, if you could, Tom.

MR. FOX: Sorry.

MR. SLATER: That's okay.

Chris, this might take a second, but could you put up Exhibit 204, please, the deviation investigation report prepared July 20, 2018? That's 20 -- oh, you know what, you have the -- that's what I want.

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BY MR. SLATER:
Q. Does this document look familiar to you? It's Exhibit 204 from a prior deposition.
A. I don't recognize it immediately.
Q. All right. Because you were saying something about some generic deviation investigation report, and you said you didn't know what it was. I'm showing you, that's the actual title of a document.
A. I understand that.
Q. It's very simple. Hang on.
A. No, it's not that simple. I reviewed other documents that contained attachments such as standard management procedures and things like that.
And when you asked me the question before, I didn't know whether this was one that might have been included in one of those other packages, or I may have seen it but just not as a standalone document.
Q. I saw no discussion of this document at all in your report. Is there

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something in there that I may have overlooked, or am I correct that you didn't discuss this document at all?
A. Not as a standalone document, no. And the data --
Q. That's all I asked you, though, so I don't need an explanation beyond that, okay?
A. Okay.
MR. SLATER: Let's go to ZHP, the last four digits are 4386, Chris. It's 22 of 33.
A. Is this the same report, or is this something different?
Q. It's the same report.
MR. SLATER: Can you blow up the bottom part, Chris, under Section 3.8 with that heading? Perfect.

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[redacted]
BY MR. SLATER:
Q. Now, you were asked some questions about ghost peaks. Do you know what a ghost peak is? Do you know how that's defined?
A. I know that they occur frequently. And as I said before, this is not something I do for a living. I've just heard the term used very often to describe unidentified peaks, they're usually not very large in terms of quantity that may arise from any of a number of different factors and require some investigation to resolve.
Q. Do you know the difference between a ghost peak and an aberrant peak?
A. No.
Q. Do you know if all unknown peaks are ghost peaks?
A. No, I think when -- you call something a ghost peak when it's not possible to define with specificity what's causing it, and there are a number of different possible contributing factors that requires an

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investigation to try to iron that out.
Q. You're guessing at the definition when you just said that, right? You don't know if you're right?
A. I'm telling you what my understanding is. If my understanding is incorrect, then so be it. But that term has been used to me for a number of years, and the context has usually been that.
Q. I'm not going to go through those FDA statements that counsel had you read, but I want to ask you a question.
There was a point where the FDA was explaining why they didn't find the problem with the NDMA in the valsartan on their inspections.
Do you remember you were reading that part?
A. Yes.
Q. You understand we're not suing the FDA here; we're suing ZHP, right?
A. Of course.
Q. Okay. And if -- rephrase. And if the manufacturer -- rephrase.

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You said in your report that the FDA primarily relies upon drug manufacturers to voluntarily follow the law, right?
A. Yes.
Q. That's how the system works, is the companies are supposed to follow the regulations and follow their SOPs so that things like this don't happen, right?
MR. FOX: Object to the form. Argumentative.
A. Yes.
MR. SLATER: Chris, let's go, if we could, to the Warning Letter, ZHP 213, the November 29, 2018 Warning Letter. Thank you.
(Whereupon, Chesney Exhibit Number 13 was marked for identification.)
BY MR. SLATER:
Q. You've seen this document, correct?
A. I have.
Q. And right there on the first

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page in the second sentence it says, "This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API)," right?
A. Yes.
Q. And then the next paragraph says, "Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, 21 USC 351(a)(2)(B)," right?
A. Yes.
Q. And then the FDA says that they reviewed the August 26, 2018 response from ZHP to the 483s, and acknowledged receipt of your subsequent correspondence, right?
A. That's right.
Q. Let's go through number 1 a little bit. "Failure of your quality unit to ensure that quality-related complaints are investigated and resolved." It says,

"Valsartan API."

You've read this paragraph, right?

A. I have. And I've also read ZHP's response to all this to get some balance to the situation.

Q. Did I ask you about ZHP's response?

A. No, you didn't.

Q. Okay. By the way, to the extent that ZHP withheld information from the FDA as part of its investigation, that would be unlawful, correct, if that information was material to the investigation?

MR. FOX: Objection to the form. Calls for a legal conclusion.

A. That's not an area that I get myself into as a rule. Whether there's been a material misrepresentation or not is -- that's usually a legal conclusion.

BY MR. SLATER:

Q. Okay. This says under number 1, "Your firm received a complaint from a customer on June 6, 2018, after an unknown

peak was detected during residual solvents testing for valsartan API manufactured at your facility. The unknown peak was identified as the probable human carcinogen N-nitrosodimethylamine (NDMA). Your investigation (DCE-18001)" -- and I'll tell you for the record that's the deviation investigation report I just showed you. If you need me to show it to you again I'll show you and show you the number matches up.

A. No, that's all right. I take your word for it.

Q. -- "determined that the presence of NDMA was caused by the convergence of three process-related factors, one factor being the use of the solvent dimethylformamide (DMF). Your investigation concluded that only one valsartan manufacturing process (referred to as the zinc chloride process in your investigation) was impacted by the presence of NDMA.

"However, FDA analyses of samples of your API, and finished drug product manufactured with your API,

identified NDMA in multiple batches manufactured with a different process, namely the trimethylamine process, which did not use the solvent DMF. These data demonstrate that your investigation was inadequate and failed to resolve the control and presence of NDMA in valsartan API distributed to customers."

Do you see what I just read?

A. Yes.

Q. You've told me you didn't evaluate the TEA process, the triethylamine process, and you didn't talk about it in your report at all, right?

A. That's correct.

[redacted]

not something you addressed at all in your report, right?

A. That was something that falls in the area of process chemistry, and I again would defer to people with the appropriate

expertise to evaluate that.

[redacted]

MR. FOX: Objection to form.

BY MR. SLATER:

Q. Wondering if you know that.

A. No, I haven't seen that information.

Q. Going back to the document now, the warning letter, it says, "Your investigation also failed:", the first bullet point, "To include other factors that may have contributed to the presence of NDMA."

Second bullet point, "To assess factors that could put your API at risk for NDMA cross-contamination.

And then the third bullet point, "To evaluate the potential for other mutagenic impurities to form in your products."

Do you see that?

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A. Yes, I do.
Q. Then the next paragraph, "Our investigation also noted other examples of your firm's inadequate investigation of unknown peaks observed in chromatograms."
Do you see that?
A. Yes.
Q. If you go to the next paragraph, it says, "Your response states that NDMA was difficult to detect. However, if you had investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA. For example, you told our investigators you were aware of a peak that eluted after the toluene peak in valsartan API residual solvent chromatograms where the presence of NDMA was expected to elute. At the time of testing, you considered this unidentified peak to be noise and investigated no further."
And then it goes through the API validation batches, and they indicate that these "show at least one unidentified

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peak eluting after the toluene peak in the area where the presence of NDMA was suspected to elute."
So I read that as a preview to this question, which is the FDA didn't think -- you would agree with me the FDA didn't think that ZHP did a good job in evaluating unknown peaks, right?
MR. FOX: Objection to form.
A. That's what the warning letter alleges, yes.
BY MR. SLATER:
Q. And then if you go to the next paragraph at the bottom of this page, page 2 of this warning letter, in the middle of it, it says, "FDA has grave concerns about the potential presence of mutagenic impurities in all intermediates and API manufactured at your facility, both because of the data indicating the presence of impurities in API manufactured by multiple processes, and because of the significant inadequacies in your investigation."
So again, there's some what the

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FDA termed grave concerns about what was going on in ZHP's facilities, right?
A. That's correct.
MR. SLATER: Now let's go to the page number 4, please, Chris.
Q. Heading number 2, "Failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API."
That's relating to the risk assessment, correct?
A. Yes.
Q. It says, "In November 2011 you approved a valsartan API process change that included the use of the solvent DMF. Your intention was to improve the manufacturing process, increase product yield, and lower production costs. However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process. Specifically, you did not consider the potential for mutagenic or other toxic impurities to form from DMF degradants, including the primary DMF degradant,

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dimethylamine. According to your ongoing investigation, dimethylamine is required for the probable human carcinogen NDMA to form during the valsartan API manufacturing process. NDMA was identified in valsartan API manufactured at your facility."
Do you see what I just read?
A. Yes.
Q. The failure to adequately assess the potential formation of mutagenic impurities when ZHP implemented the new process, that would be a cGMP violation, correct?
MR. FOX: Objection to form.
A. I think you used the word "potential." That's not what it says, but...
BY MR. SLATER:
Q. It says "potential formation." It says, "However, you failed to adequately assess the potential formation of mutagenic impurities when you implemented the new process."
And my question to you is, the failure to adequately assess the potential

formation of the mutagenic impurities, that's a violation of cGMP, right?

MR. FOX: Objection to form.

BY MR. SLATER:

Q. If that's what happened, it's a violation, correct?

MR. FOX: Objection to form.

A. I'm sorry, I lost you as you were reading. You must have skipped ahead somewhere and I was reading the wrong sentence.

Can you direct me where you're reading?

BY MR. SLATER:

Q. I'm in the first paragraph under number 2, the third line.

A. Oh, okay.

Q. It says, "However, you failed to adequately assess" --

A. Okay. I'm sorry. I skipped ahead to far.

Q. No problem.

You see it says, "However, you failed to adequately assess the potential

formation of mutagenic impurities when you implemented the new process"?

A. Yes.

Q. That would be a cGMP violation, right?

MR. FOX: Objection to form.

THE WITNESS: I'm sorry, what did you say?

MR. FOX: I objected to the form.

What was the answer?

MR. SLATER: You talked over it, that's why I'm asking him.

BY MR. SLATER:

Q. Is that correct?

A. Yes, that's correct.

Q. Going now to the second paragraph under section -- the heading section 2, "You also failed to evaluate the need for additional analytical methods to ensure that unanticipated impurities were appropriately detected and controlled in your valsartan API before you approved the process change."

Stopping right there, that's a cGMP violation, correct?

MR. FOX: Objection to the form.

A. That should be done, yes.

BY MR. SLATER:

Q. It says further, I'm going to continue to read, "You are responsible for developing and using suitable methods to detect impurities when developing, and making changes to, your manufacturing processes. If new or higher levels of impurities are detected, you should fully evaluate the impurities and take action to ensure the drug is safe for patients."

You agree with that statement, that was an obligation of ZHP, right?

MR. FOX: Objection to the form.

A. I agree that's a correct statement.

BY MR. SLATER:

Q. Go to the next paragraph.

It says, "Your response" -- now

they're talking about that response that you were telling me about before, that you got that long response from ZHP and you read it. Remember you told me that?

A. Wait. There are two responses. The one they're referring to here is a response to the 483.

There's also a response to this warning letter where they take issue with a number of these points, provide additional data, and a considerable level of detail.

So this letter by itself makes certain assertions, but it's not the complete story.

Q. Looking now at the third paragraph, the FDA says, "Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree."

MR. FOX: Adam, let me object. Where are you, Adam?

MR. SLATER: Third paragraph

under number 2. I wasn't planning to do any of this, you brought it up, so I'm just going to hammer the nail.
BY MR. SLATER:
Q. Third paragraph under number 2, I'll go back to it again. "Your response" -- rephrase.
The third paragraph under number 2 says, "Your response states that predicting NDMA formation during the valsartan manufacturing process required an extra dimension over current industry practice, and that your process development study was adequate. We disagree."
Do you see that?
A. I do.
Q. So the FDA felt that the process development study was inadequate and there was a violation of cGMP, correct?
MR. FOX: Objection to form.
A. They -- I don't agree with your statement there, and it's inconsistent with their public statements both before and after this warning letter. But that's what they

say.
BY MR. SLATER:
Q. Coming back to my question, the FDA disagreed with ZHP that they couldn't have known about the potential formation of the NDMA, right?
MR. FOX: Objection to form.
A. They disagreed that it required an extra dimension over current industry practice. That's what the reference is to.
BY MR. SLATER:
Q. The next sentence says, "We remind you that common industry practice may not always be consistent with CGMP requirements and that you are responsible for the quality of drugs you produce."
You agree with that statement, right?
A. I do.
Q. So when ZHP decided to develop this zinc chloride process that had not been used before, they were responsible for the quality of the drugs that would be manufactured with that new process, right?

MR. FOX: Objection to form.
A. Yes, they were responsible.
BY MR. SLATER:
Q. And the fact that nobody else had been manufacturing by that process previously doesn't change the fact or excuse the fact that they failed to evaluate fully the risks from that new process?
MR. FOX: Objection to form.
A. The fact that nobody else was using the process does not relieve them of the necessity to evaluate it fully.
MR. SLATER: Okay. Let's take that down. Let's go, Chris, if we could, to Exhibit 212.
(Whereupon, Chesney Exhibit Number 14 was marked for identification.)
BY MR. SLATER:
Q. This was previously marked as Exhibit 212 at a deposition of Peng Dong. I assume you haven't seen this. It's a draft of a deviation investigation report.
A. From the cover page I couldn't

tell you.
And could you make it a little bit larger? It's a little small on my screen.
Q. No problem.
A. The cover page I don't recognize, but I don't know.
Q. Well, I'm going to represent to [redacted]
Do you see what I just read?

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A. Yes.
Q. And if that's what happened, that was a violation of cGMP, as we've gone through earlier, correct?
MR. FOX: Objection to form.
A. Again, I can't characterize an individual occurrence like that as a violation or not a violation. That requires a lot more consideration.
But it's concerning and certainly worthy of everyone's attention, including those at the company that received this report.
MR. SLATER: Take that down.
The next thing I'd like to go to, if we could, is -- I believe it was Exhibit 430. It's the August 26, 2018 response to the 483 letter.
(Whereupon, Chesney Exhibit Number 15 was marked for identification.)
MR. SLATER: Signed by Jun Du.
MR. GEDDIS: Give me a second.
THE VIDEOGRAPHER: Excuse me,

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Attorney Slater?
MR. SLATER: Yes.
THE VIDEOGRAPHER: May we go off the record for a moment? I have approximately ten minutes left on this backup media recording.
MR. SLATER: No, I want to continue. We'll be done in ten minutes. I'm also through.
THE VIDEOGRAPHER: Okay, sir.
MR. SLATER: Don't worry about it. If I start to run into it and get to two minute, let me know.
THE VIDEOGRAPHER: The Zoom is going, just the backup.
MR. SLATER: Are we okay?
THE VIDEOGRAPHER: The Zoom is recording, yes. The backup media had approximately ten minutes left.
MR. SLATER: Okay. Just let me know if we get to two minutes.
THE VIDEOGRAPHER: Okay, sir.
MR. SLATER: While Chris is looking for that, you might as well --

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okay. He got it.
BY MR. SLATER:
Q. Okay. This is the August 26, 2018 letter from Jun Du of ZHP to the FDA.
You've seen this, correct?
A. Yes, I have.
Q. Let's go to page 3 of 4, please.
MR. SLATER: And let's blow up that middle paragraph, if we could, just so we can all see it. Okay. Perfect.

MR. FOX: Objection to the form.

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A. You showed me a document that had a suggestion of that. But as I indicated, it's got some technical aspects that I'm not comfortable evaluating, and would trigger a lot more questions in my mind before I would be prepared to make a definitive statement about it.
BY MR. SLATER:
Q. The July 2017 e-mail doesn't make any suggestion, it states definitively that there's NDMA in valsartan, the root cause is the quenching of the sodium azide in the presence of sodium nitrite, and says it's a problem with all the sartans, across sartans. That's what it says. It doesn't speculate about it; it makes those factual statements, right?
MR. FOX: Objection. Object to the form. Argumentative.
A. It presents the information in that way, yes.
BY MR. SLATER:
Q. All of which you can tell me sitting right now is accurate because we know

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historically that was all proven true, those factual statements, right?
MR. FOX: Objection to the fact -- objection to the form.
A. Most of that proved to be correct. But again, putting myself in the position of having received that at that point in time, I would have had a host of more questions.
BY MR. SLATER:
Q. It's not some of it has been proven correct, all of those three things have been proven correct, right?
MR. FOX: Objection to the form. Argumentative.
A. I, at this point, am not sure specifically what we're talking about in terms of all of them.
BY MR. SLATER:
Q. There's NDMA in valsartan, it's caused when they quench the sodium azide with sodium nitrite, and it's a problem with multiple sartans. That's been proven true, right?

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MR. FOX: Objection to the form.
A. Yes. At a high level, yes, that's true.
BY MR. SLATER:
Q. And just to be clear, Jun Du represented that this wasn't learned until June of 2018. That's what he represented to the FDA, right?
MR. FOX: Objection to form. Argumentative, document speaks for itself.
MR. SLATER: All right. Look, I'll ask it again.
BY MR. SLATER:
Q. It's a fact that ZHP has always represented to the FDA that those facts weren't learned until June 2018, right?
MR. FOX: Well, ask the question.
BY MR. SLATER:
Q. Can you answer that? That's correct, right?
A. I'm sorry, I heard two people

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talking there. I wasn't sure where we were with this.
Could you restate the question, because I heard multiple people.
Q. Sure.
ZHP has always told the FDA it did not learn of what we just talked about until June of 2018 at the earliest, right?
A. That's when they reached the final conclusion, yes. That's what they told the FDA.
Q. Well, they claimed that they didn't even know there was NDMA in the valsartan until June of 2018, right?
MR. FOX: Objection to form.
A. That they -- they wouldn't have said they knew it until they were sure of it.
MR. SLATER: Let's take that down and go to Exhibit 312, the establishment inspection report.
(Whereupon, Chesney Exhibit Number 16 was marked for identification.)
MR. SLATER: Do we have at

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least another five minutes left on that backup? Okay.
BY MR. SLATER:
Q. Here on the screen we have the Establishment Inspection Report, Exhibit 312.
Do you see that?
A. Yes.
Q. And I just want to go to page 20 of 58. Looking at the paragraph that says, "During the opening presentation."
MR. SLATER: Let's blow that up a little bit. Perfect.
Q. This states, "During the opening presentation on July 23, 2018, Mr. Du explained how the firm came to know Valsartan manufactured by the firm could contain the genotoxic impurity NDMA. Mr. Du stated Novartis placed an order with the firm for 45 Metric Tons of valsartan." And then he goes through it and talks about how it was Novartis that told ZHP of this issue, right?
A. Let me read the paragraph here.
(Witness reviewing document.)
A. Okay. So okay, I've read the

paragraph. Now, what was the question again?
Q. This is reciting what Jun Du told the FDA at the time of the inspection of July 23, 2018, right?
A. Yes.
Q. Based on the content of the e-mail from July of 2017 showing that ZHP already knew there was NDMA in the valsartan and why it was occurring, when Mr. Du spoke to the FDA that day, he lied to the FDA, correct?
MR. FOX: Objection. Calls for conclusion, speculation.
A. I can't conclude that based on what I see here.
BY MR. SLATER:
Q. What Jun Du told the FDA was untrue in comparison to what that July 2017 e-mail shows, correct?
MR. FOX: Objection to form. Beyond his expert report, calls for a legal conclusion.
A. Again, I am still not confident of the state of the firm's awareness,

notwithstanding Dr. Lin's statement in his July 17th e-mail. For me to accept that as fact, I would need to see considerably more backup information that that statement is based upon and have it evaluated by scientific experts to be sure it's right.
Because an allegation such as that that he was not being truthful is very serious and needs to be vetted in considerable detail, and I think FDA would approach it the same way.
BY MR. SLATER:
Q. If ZHP wasn't truthful with the FDA as to when they learned there was NDMA in the valsartan and how it was occurring, if that occurred, that's a very, very serious violation, right?
MR. FOX: Objection. Asked and answered.
A. Yes, that would be a significant violation, yes.
MR. SLATER: I don't have any other questions unless your counsel wants to ask you more.

FURTHER EXAMINATION
BY MR. FOX:
Q. Mr. Chesney, can something that occurred in this instance with impurity found in valsartan, could that have occurred even though everyone followed the law?
MR. SLATER: Objection.
A. Yes.
BY MR. FOX:
Q. In regard to GMP and cGMP, what does the "C" stand for?
A. Current.
Q. Does cGMP change over time?
A. Yes.
Q. Did cGMP change with regard to nitrosamines in the 2019 time frame as far as the FDA is concerned?
MR. SLATER: Objection.
A. I would draw that conclusion from the public statements that we looked at earlier, 2018 and 2019, that as information was developed and better understood, the expectations rose and were still, in fact, rising at the time of the January 25, 2019

statement.
BY MR. FOX:
Q. And when cGMP changes, does the FDA typically apply it retroactively to the industry?
MR. SLATER: Objection.
You can answer.
A. No.
BY MR. FOX:
Q. That would be unfair, wouldn't it?
MR. SLATER: Objection.
You can answer.
A. Yes, it would be unfair, and that has not been the practice, to my knowledge.
MR. FOX: No further questions.
MR. SLATER: I don't have any other questions.
MR. FOX: Thank you, Mr. Chesney.
Thank you, Adam.
MR. SLATER: Thank you very much.

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THE WITNESS: Thank you, Mr. Slater.

MR. SLATER: It was nice to meet you. I hope everybody has a nice evening.

THE WITNESS: Thank you. Same to you, sir.

THE VIDEOGRAPHER: The time is 5:03 p.m. We're off the record. This concludes today's deposition.

(Whereupon, the deposition was concluded.)

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CERTIFICATE

I, MAUREEN O'CONNOR POLLARD, Registered Diplomate Reporter, Realtime Systems Administrator, and Certified Shorthand Reporter, do hereby certify that prior to the commencement of the examination, DAVID L. CHESNEY, was remotely duly identified and sworn by me to testify to the truth, the whole truth, and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by and before me at the time, place, and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.

____

MAUREEN O'CONNOR POLLARD
NCRA Registered Diplomate Reporter
Realtime Systems Administrator
Certified Shorthand Reporter
Notary Public

Dated: March 24, 2022

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INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it. It will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

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E R R A T A

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ACKNOWLEDGMENT OF DEPONENT

I, ___________________________, do Hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

____
DAVID L. CHESNEY DATE

Subscribed and sworn
To before me this
_______ day of __________________, 20____.

My commission expires: _________________

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Notary Public

LAWYER'S NOTES

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Exhibit 55

General Notices and Requirements

Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia

General Notices and Requirements

Change to read:

• The *General Notices and Requirements* section (the *General Notices*) presents the basic assumptions, definitions, and default conditions for the interpretation and application of the *United States Pharmacopeia* (*USP*) and the *National Formulary* (*NF*).

Requirements stated in these *General Notices* apply to all articles recognized in the *USP* and *NF* (the "compendia") and to all general chapters unless specifically stated otherwise. Where the requirements of an individual monograph differ from the *General Notices* or a general chapter, the monograph requirements apply and supersede the requirements of the *General Notices* or the general chapter, whether or not the monograph explicitly states the difference.

1. TITLE AND REVISION

The full title of this publication (consisting of three volumes and including its *Supplements*), is *The Pharmacopeia of the United States of America*, Thirty-Second Revision and the *National Formulary*, Twenty-Seventh Edition. These titles may be abbreviated to *United States Pharmacopeia*, Thirty-Second Revision (or to *USP 32*), to *NF 27*, and to *USP 32–NF 27*. The *United States Pharmacopeia*, Thirty-Second Revision, and the *National Formulary*, Twenty-Seventh Edition, supersede all earlier revisions. Where the terms "*USP*," "*NF*," or "*USP–NF*" are used without further qualification during the period in which these compendia are official, they refer only to *USP 32*, *NF 27*, and any *Supplement(s)* thereto. The same titles, with no further distinction, apply equally to print or electronic presentation of these contents. Although *USP* and *NF* are published under one cover and share these *General Notices*, they are separate compendia.

This revision is official beginning May 1, 2009, unless otherwise indicated in specific text.

Supplements to *USP* and *NF* are published periodically.

Interim Revision Announcements are revisions to *USP* and *NF* that are published in *Pharmacopeial Forum*. *Interim Revision Announcements* contain official revisions and their effective dates, announcements of the availability of new USP Reference Standards, and announcements of tests or procedures that are held in abeyance pending availability of required USP Reference Standards.

Revision Bulletins are revisions to official text or postponements that require expedited publication. They are published on the USP website and generally are official immediately unless otherwise specified in the *Revision Bulletin*.

Errata are corrections to items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirements. *Errata* are effective upon publication.

2. OFFICIAL STATUS AND LEGAL RECOGNITION

2.10. Official Text

Official text is text contained in *USP* and *NF*, including monographs, general chapters, and these *General Notices*. Revisions to official text are provided in *Supplements*, *Interim Revision Announcements*, and *Revision Bulletins*. General chapters numbered from 1000 to 1999 are considered interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no mandatory requirements applicable to any official article unless specifically referenced in these *General Notices*, a monograph, or a general chapter numbered below 1000. General chapters numbered above 2000 apply only to articles that are intended for use as dietary ingredients and dietary supplements.

2.20. Official Articles

An *official article* is an article that is recognized in *USP* or *NF*. An article is deemed to be recognized and included in a compendium when a monograph for the article is published in the compendium and an official date is generally or specifically assigned to the monograph.

The title specified in a monograph is the *official title* for such article. Other names considered to be synonyms of the official titles may not be used as substitutes for official titles.

Official articles include both *official substances* and *official products*. An *official substance* is a drug substance, excipient, dietary ingredient, other ingredient, or component of a finished device for which the monograph title includes no indication of the nature of the finished form.

An *official product* is a drug product, dietary supplement, compounded preparation, or finished device for which a monograph is provided.

2.30. Legal Recognition

The *USP* and *NF* are recognized in the laws and regulations of many countries throughout the world. Regulatory authorities may enforce the standards presented in the *USP* and *NF*, but because recognition of the *USP* and *NF* may vary by country, users should understand applicable laws and regulations. More information about the legal status of the *USP* and *NF* is provided in the *Mission and Preface*.

3. CONFORMANCE TO STANDARDS

3.10. Applicability of Standards

Standards for an article recognized in a USP compendium are expressed in the article's monograph, applicable general chapters, and these *General Notices*. Unless specifically exempted elsewhere in a compendium, the identity, strength, quality, and purity of an article are determined by the official tests, procedures, and acceptance criteria, whether incorporated in the monograph itself, in the *General Notices*, or in the applicable general chapters.

The standards in the relevant monograph, general chapter(s), and *General Notices* apply at any time in the life of the article from production to expiration. The manufacturer's specifications, and good manufacturing practices generally, are developed and followed to ensure that the article will comply with compendial standards until its expiration date, when stored as directed. Thus, any official article tested as directed in the relevant monograph shall comply.

At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. First-party (manufacturer), second-party (buyer), or third-party (regulator) compliance testing may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies.

Official products other than dietary supplements are prepared from ingredients that meet *USP* or *NF* standards, where standards for such ingredients exist.

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to ensure that the resultant substances meet the requirements of the compendial monographs.

3.10.10. Applicability of Standards to Drug Products, Drug Substances, and Excipients

The applicable *USP* or *NF* standard applies to any article marketed in the United States that (1) is recognized in the compendium and (2) is intended or labeled for use as a drug or as an ingredient in a drug. The applicable standard applies to such articles whether or not the added designation "USP" or "NF" is used. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles.

3.10.20. Applicability of Standards to Medical Devices, Dietary Supplements, and Their Components and Ingredients

An article recognized in *USP* or *NF* shall comply with the compendial standards if the article is a medical device, component intended for a medical device, dietary supplement, dietary ingredient, or other ingredient that is intended for incorporation into a dietary supplement, and is labeled as conforming to the *USP* or *NF*.

Generally, dietary supplements are prepared from ingredients that meet *USP*, *NF*, or *Food Chemicals Codex* standards. Where such standards do not exist, substances may be used in dietary supplements if they have been shown to be of acceptable food grade quality using other suitable procedures.

3.20. Indicating Conformance

A drug product, drug substance, or excipient may use the designation "USP" or "NF" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the identity prescribed in the specified compendium.

When a drug product, drug substance, or excipient differs from the relevant *USP* or *NF* standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.

When a drug product, drug substance, or excipient fails to comply with the identity prescribed in *USP* or *NF* or contains an added substance that interferes with the prescribed tests and procedures, the article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in *USP* or *NF*.

A medical device, dietary supplement, or ingredient or component of a medical device or dietary supplement may use the designation "USP" or "NF" in conjunction with its official title or elsewhere on the label only when (1) a monograph is provided in the specified compendium and (2) the article complies with the monograph standards and other applicable standards in the compendium.

The designation "USP" or "NF" on the label may not and does not constitute an endorsement by USP and does not represent assurance by USP that the article is known to comply with the relevant standards. USP may seek legal redress if an article purports to be or is represented as an official article in one of USP's compendia and such claim is determined by USP not to be made in good faith.

The designation "*USP–NF*" may be used on the label of an article provided that the label also bears a statement such as "Meets *NF* standards as published by USP," indicating the particular compendium to which the article purports to apply.

When the letters "USP," "NF," or "USP–NF" are used on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article. The letters are not to be enclosed in any symbol such as a circle, square, etc., and shall appear in capital letters.

If a dietary supplement does not comply with all applicable compendial requirements but contains one or more dietary ingredients or other ingredients that are recognized in *USP* or *NF*, the individual ingredient(s) may be designated as complying with *USP* or *NF* standards or being of *USP* or *NF* quality provided that the designation is limited to the individual ingredient(s) and does not suggest that the dietary supplement complies with *USP* standards.

4. MONOGRAPHS AND GENERAL CHAPTERS

4.10. Monographs

Monographs set forth the article's name, definition, specification, and other requirements related to packaging, storage, and labeling. The specification consists of tests, procedures, and acceptance criteria that help ensure the identity, strength, quality, and purity of the article. For general requirements relating to specific monograph sections, see section 5, *Monograph Components*.

Because monographs may not provide standards for all relevant characteristics, some official substances may conform to the *USP* or *NF* standard but differ with regard to nonstandardized properties that are relevant to their use in specific preparations. To assure interchangeability in such instances, users may wish to ascertain functional equivalence or determine such characteristics before use.

4.10.10. Applicability of Test Procedures

A single monograph may include several different tests, procedures, and/or acceptance criteria that reflect attributes of different manufacturers' articles. Such alternatives may be presented for different polymorphic forms, impurities, hydrates, and dissolution cases. Monographs indicate the tests, procedures, and/or acceptance criteria to be used and the required labeling.

4.10.20. Acceptance Criteria

The acceptance criteria allow for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. The existence of compendial acceptance criteria does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" compendial quality. Similarly, the fact that an article has been prepared to tighter criteria than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the compendial requirements.

An official product shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. Where the minimum amount of a substance present in a dietary supplement is required by law to be higher than the lower acceptance criterion allowed for in the monograph, the upper acceptance criterion contained in the monograph may be increased by a corresponding amount.

The acceptance criteria specified in individual monographs and in the general chapters for compounded preparations are based on such attributes of quality as might be expected to characterize an article compounded from suitable bulk drug substances and ingredients, using the procedures provided or recognized principles of good compounding practice, as described in these compendia.

4.20. General Chapters

Each general chapter is assigned a number that appears in angle brackets adjacent to the chapter name (e.g., *Chromatography* ⟨621⟩). General chapters may contain the following:

- Descriptions of tests and procedures for application through individual monographs,
- Descriptions and specifications of conditions and practices for pharmaceutical compounding,
- General information for the interpretation of the compendial requirements,
- Descriptions of general pharmaceutical storage, dispensing, and packaging practices, or
- General guidance to manufacturers of official substances or official products.

When a general chapter is referenced in a monograph, acceptance criteria may be presented after a colon.

Some chapters may serve as introductory overviews of a test or of analytical techniques. They may reference other general chapters that contain techniques, details of the procedures, and, at times, acceptance criteria.

5. MONOGRAPH COMPONENTS

5.10. Molecular Formula

The use of the molecular formula for the active ingredient(s) named in defining the required strength of a compendial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

5.20. Added Substances, Excipients, and Ingredients

Substances are regarded as unsuitable for inclusion in an official article and therefore prohibited unless: (1) they do not exceed the minimum quantity required for providing their intended effect; (2) their presence does not impair the bioavailability, therapeutic efficacy, or safety of the official article; and (3) they do not interfere with the assays and tests prescribed for determining compliance with the compendial standards.

The air in a container of an official article may, where appropriate, be evacuated or be replaced by carbon dioxide, helium, argon, or nitrogen, or by a mixture of these gases. The use of such gas need not be declared in the labeling.

5.20.10. Added Substances, Excipients, and Ingredients in Official Substances

Official substances may contain only the specific added substances that are permitted by the individual monograph. Where such addition is permitted, the label shall indicate the name(s) and amount(s) of any added substance(s).

5.20.20. Added Substances, Excipients, and Ingredients in Official Products

Suitable substances and excipients such as antimicrobial agents, pharmaceutical bases, carriers, coatings, flavors, preservatives, stabilizers, and vehicles may be added to an official product to enhance its stability, usefulness, or elegance, or to facilitate its preparation, unless otherwise specified in the individual monograph.

Added substances and excipients employed solely to impart color may be incorporated into official products other than those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the U.S. Food and Drug Administration (FDA), provided such added substances or excipients are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

The proportions of the substances constituting the base in ointment and suppository products and preparations may be varied to maintain a suitable consistency under different climatic conditions, provided that the concentrations of active ingredients are not varied and provided that the bioavailability, therapeutic efficacy, and safety of the preparation are not impaired.

5.20.20.1. In Compounded Preparations

Compounded preparations for which a complete composition is given shall contain only the ingredients named in the formulas unless specifically exempted herein or in the individual monograph. Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process.

Where a monograph for a compounded preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried before use if due allowance is made for the water or other volatile substances present in the quantity taken.

Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of official preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A preparation that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a usual ingredient in the preparation or a permissible added substance; in either case the denaturant shall be identified on the label of the topical preparation. Where a process is given in the individual monograph, any preparation compounded using denatured alcohol shall be identical to that prepared by the monograph process.

5.20.20.2. In Dietary Supplements

Additional ingredients may be added to dietary supplement products provided that the additional ingredients: (1) comply with applicable regulatory requirements; and (2) do not interfere with the assays and tests prescribed for determining compliance with compendial standards.

5.30. Description and Solubility

Only where a quantitative solubility test is given in a monograph and is designated as such is it a test for purity.

A monograph may include information regarding the article's description. Information about an article's "description and solubility" also is provided in the reference table *Description and Relative Solubility of USP and NF Articles*. The reference table merely denotes the properties of articles that comply with monograph standards. The reference table is intended primarily for those who use, prepare, and dispense drugs and/or related articles. Although the information provided in monographs and the information in the reference table may indirectly assist in the preliminary evaluation of an article, it is not intended to serve as a standard or test for purity.

The approximate solubility of a compendial substance is indicated by one of the following descriptive terms:

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

5.40. Identification Test

The compendial test titled *Identification* is provided as an aid in verifying the identity of articles as they are purported to be, e.g., those taken from labeled containers. Tests presented in the *Identification* section shall be used to assist in establishing the identity of the substance but are not necessarily sufficient to establish proof of identity. Other tests and specifications in the monograph often are necessary to establish or confirm the identity of an article. Failure of an article to meet the requirements of a prescribed *Identification* test may indicate that the article is mislabeled.

5.50. Assay

Assay tests for compounded preparations are not intended for evaluating a compounded preparation before dispensing, but instead are intended to serve as the official test in the event of a question or dispute regarding the preparation's conformance to official standards.

5.50.10. Units of Potency (Biological)

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as "USP Units." For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined (see *Biologics* ⟨1041⟩).

5.60. Impurities and Foreign Substances

Tests for the presence of impurities and foreign substances are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

Nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in the processing methods or that may be introduced from external sources should be employed in addition to the tests provided in the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practice.

5.60.10. Other Impurities in *USP* and *NF* Articles

If a *USP* or *NF* monograph includes an assay or organic impurity test based on chromatography, other than a test for residual solvents, and that monograph procedure does not detect an impurity present in the substance, the amount and identity of the impurity, where both are known, shall be stated in the labeling (certificate of analysis) of the official substance, under the heading *Other Impurity(ies)*.

The presence of any unlabeled other impurity in an official substance is a variance from the standard if the content is 0.1% or greater. The sum of all *Other Impurities* combined with the monograph-detected impurities may not exceed 2.0% (see *Ordinary Impurities* ⟨466⟩), unless otherwise stated in the monograph.

The following categories of drug substances are excluded from *Other Impurities* requirements:

- fermentation products and semi-synthetics derived therefrom,
- radiopharmaceuticals,
- biologics,
- biotechnology-derived products,
- peptides,
- herbals, and
- crude products of animal or plant origin.

Any substance known to be toxic shall not be listed under *Other Impurities*.

5.60.20. Residual Solvents in *USP* and *NF* Articles

All *USP* and *NF* articles are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. If solvents are used during production, they must be of suitable quality. In addition, the toxicity and residual level of each solvent shall be taken into consideration, and the solvents limited according to the principles defined and the requirements specified in *Residual Solvents* ⟨467⟩, using the general methods presented therein or other suitable methods.

5.70. Performance Tests

Where content uniformity determinations have been made using the same analytical methodology specified in the *Assay*, with appropriate allowances made for differences in sample preparation, the average of all of the individual content uniformity determinations may be used as the *Assay* value.

5.80. USP Reference Standards

USP Reference Standards are authentic specimens that have been approved by the USP Reference Standards Expert Committee as suitable for use as comparison standards in *USP* or *NF* tests and assays. (See *USP Reference Standards* ⟨11⟩.) Current official lots of USP Reference Standards are published in the *USP Reference Standards Catalog*. Where a procedure calls for the use of a compendial article rather than for a USP Reference Standard as a material standard of reference, a substance meeting all of the compendial monograph requirements for that article shall be used. No new *USP* or *NF* standard or procedure requiring the use of a new USP Reference Standard shall be official until the specified USP Reference Standard is available.

Unless a reference standard label bears a specific potency or content, assume the reference standard is 100.0% pure in the official application. Unless otherwise directed in the procedure in the individual monograph or in a general chapter, USP Reference Standards are to be used in accordance with the instructions on the label of the Reference Standard.

6. TESTING PRACTICES AND PROCEDURES

6.10. Safe Laboratory Practices

In performing compendial procedures, safe laboratory practices shall be followed, including precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures used. Before undertaking any procedure described in the compendia, the analyst should be aware of the hazards associated with the chemicals and the techniques and means of protecting against them. These compendia are not designed to describe such hazards or protective measures.

6.20. Automated Procedures

Automated and manual procedures employing the same basic chemistry are considered equivalent.

6.30. Alternative and Harmonized Methods and Procedures

Alternative methods and/or procedures may be used if they provide advantages in terms of accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction, or in other special circumstances. Such alternative procedures and methods shall be validated as described in the general chapter *Validation of Compendial Procedures* ⟨1225⟩ and must be shown to give equivalent or better results. Only those results obtained by the methods and procedures given in the compendium are conclusive.

Alternative procedures should be submitted to USP for evaluation as a potential replacement or addition to the standard (see section 4.10, *Monographs*).

Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method or procedure from one of these pharmacopeias, it should comply with the requirements of the *USP*. When a difference appears, or in the event of dispute, only the result obtained by the method and/or procedure given in the *USP* is conclusive.

6.40. Dried, Anhydrous, Ignited, or Solvent-Free Basis

All calculations in the compendia assume an "as-is" basis unless otherwise specified.

Test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying*, or *Water*, or *Loss on ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

The term "solvent-free" signifies that the calculation shall be corrected for the presence of known solvents as determined using the methods described in *Residual Solvents* ⟨467⟩ unless a test for limit of organic solvents is provided in the monograph.

The term "previously dried" without qualification signifies that the substance shall be dried as directed under *Loss on Drying* ⟨731⟩ or *Water Determination* ⟨921⟩ (gravimetric determination).

Where drying in vacuum over a desiccant is directed, a vacuum desiccator, a vacuum drying pistol, or other suitable vacuum drying apparatus shall be used.

6.40.10. Ignite To Constant Weight

"Ignite to constant weight" means that ignition shall be continued at 800 ± 25°, unless otherwise indicated, until two consecutive weighings, the second of which is taken after an additional period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.40.20. Dried To Constant Weight

"Dried to constant weight" means that drying shall be continued until two consecutive weighings, the second of which is taken after an additional drying period appropriate to the nature and quantity of the residue, do not differ by more than 0.50 mg per g of substance taken.

6.50. Preparation of Solutions

6.50.10. Filtration

Where a procedure gives direction to "filter" without further qualification, the liquid shall be passed through suitable filter paper or equivalent device until the filtrate is clear. Due to the possibility of filter effects, the initial volumes of a filtrate may be discarded.

6.50.20. Solutions

Unless otherwise specified, all solutions shall be prepared with Purified Water. Solutions for quantitative measures shall be prepared using accurately weighed or accurately measured analytes (see section 8.20, *About*).

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid shall be diluted with, or 1 part *by weight* of a solid shall be dissolved in, a sufficient quantity of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*. An expression such as "(20 : 5 : 2)" means that the respective numbers of parts, by volume, of the designated liquids shall be mixed, unless otherwise indicated.

6.50.20.1. Adjustments to Solutions

When a specified concentration is called for in a procedure, a solution of other normality or molarity may be used, provided that allowance is made for the difference in concentration and that the change does not increase the error of measurement.

Unless otherwise indicated, analyte concentrations shall be prepared to within ten percent (10%) of the indicated value. In the special case in which a procedure is adapted to the working range of an instrument, solution concentrations may differ from the indicated value by more than ten percent (10%), with appropriate changes in associated calculations. Any changes shall fall within the validated range of the instrument.

When adjustment of pH is indicated with either an acid or base and the concentration is not indicated, appropriate concentrations of that acid or base may be used.

6.50.20.2. Test Solutions

Information on Test Solutions (TS) is provided in the *Test Solutions* portion of the *Reagents, Indicators, and Solutions* section of

the *USP–NF*. Use of an alternative Test Solution or a change in the Test Solution used may require validation.

6.50.20.3. Indicator Solutions

Where a procedure specifies the use of an indicator TS, approximately 0.2 mL, or 3 drops, of the solution shall be added unless otherwise directed.

6.60. Units Necessary to Complete a Test

Unless otherwise specified, a sufficient number of units to ensure a suitable analytical result shall be taken.

6.60.10. Tablets

Where the procedure of a Tablet monograph directs to weigh and finely powder not fewer than a given number of Tablets, a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered Tablets taken shall be representative of the whole Tablets and shall, in turn, be weighed accurately.

6.60.20. Capsules

Where the procedure of a Capsule monograph gives direction to remove, as completely as possible, the contents of not fewer than a given number of the Capsules, a counted number of Capsules shall be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken shall be representative of the contents of the Capsules and shall, in turn, be weighed accurately.

6.70. Reagents

The proper conduct of the compendial procedures and the reliability of the results depend, in part, upon the quality of the reagents used in the performance of the procedures. Unless otherwise specified, reagents conforming to the specifications set forth in the current edition of *Reagent Chemicals* published by the American Chemical Society (ACS) shall be used. Where such ACS reagent specifications are not available or where the required purity differs, compendial specifications for reagents of acceptable quality are provided (see the *Reagents, Indicators, and Solutions* section of the *USP–NF*). Reagents not covered by any of these specifications should be of a grade suitable to the proper performance of the method of assay or test involved.

Listing of these reagents, including the indicators and solutions employed as reagents, in no way implies that they have therapeutic utility; furthermore, any reference to *USP* or *NF* in their labeling shall include also the term "reagent" or "reagent grade." USP may supply reagents if they otherwise may not be generally commercially available.

6.80. Equipment

Unless otherwise specified, a specification for a definite size or type of container or apparatus in a procedure is given solely as a recommendation. Other dimensions or types may be used if they are suitable for the intended use.

6.80.10. Apparatus for Measurement

Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed.

6.80.10.1. Pipet

Where a pipet is specified, a suitable buret may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

6.80.10.2. Light Protection

Where low-actinic or light-resistant containers are specified, either containers specially treated to protect contents from light or clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

6.80.20. Instrumental Apparatus

An instrument may be substituted for the specified instrument if the substitute uses the same fundamental principles of operation and is of equivalent or greater sensitivity and accuracy. These characteristics shall be qualified as appropriate. Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification.

6.80.20.1. Chromatographic Tubes and Columns

The term "diameter" refers to internal diameter (ID).

6.80.20.2. Tubing

The term "diameter" refers to outside diameter (OD).

6.80.20.3. Steam Bath

Where use of a steam bath is directed, use actively flowing steam or another regulated heat source controlled at an equivalent temperature.

6.80.20.4. Water Bath

A water bath requires vigorously boiling water unless otherwise specified.

7. TEST RESULTS

7.10. Interpretation of Requirements

Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated acceptance criteria to determine whether the article conforms to compendial requirements.

The reportable value, which often is a summary value for several individual determinations, is compared with the acceptance criteria. The reportable value is the end result of a completed measurement procedure, as documented.

Where acceptance criteria are expressed numerically herein through specification of an upper and/or lower limit, permitted values include the specified values themselves, but no values outside the limit(s). Acceptance criteria are considered significant to the last digit shown.

7.10.10. Equivalence Statements in Titrimetric Procedures

The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, the number of significant figures in the concentration of the titrant should be understood to correspond to the number of significant figures in the weight of the analyte. Corrections to calculations based on the blank determination are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

7.20. Rounding Rules

The observed or calculated values shall be rounded off to the number of decimal places that is in agreement with the limit expression. Numbers should not be rounded until the final calculations for the reportable value have been completed. Intermediate calculations (e.g., slope for linearity) may be rounded for reporting purposes, but the original (not rounded) value should be used for any additional required calculations. Acceptance criteria are fixed numbers and are not rounded.

When rounding is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is equal to or greater than 5, it is eliminated and the preceding digit is increased by 1.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3 ppm	3.5 ppm	4 ppm	No
	3.4 ppm	3 ppm	Yes
	2.5 ppm	3 ppm	Yes

8. TERMS AND DEFINITIONS

8.10. Abbreviations

- RS refers to a USP Reference Standard.
- CS refers to a Colorimetric Solution.
- TS refers to a Test Solution.
- VS refers to a Volumetric Solution that is standardized in accordance with directions given in the individual monograph or in the *Reagents, Indicators, and Solutions* section of *USP–NF*.

8.20. About

"About" indicates a quantity within 10%.

If the measurement is stated to be "accurately measured" or "accurately weighed," follow the statements in the general chapters *Volumetric Apparatus* ⟨31⟩ and *Weights and Balances* ⟨41⟩, respectively.

8.30. Alcohol Content

Percentages of alcohol, such as those under the heading *Alcohol content*, refer to percentage by volume of C_2H_5OH at 15.56°. Where a formula, test, or assay calls for alcohol, ethyl alcohol, or ethanol, the *USP* monograph article Alcohol shall be used. Where reference is made to "C_2H_5OH," absolute (100 percent) ethanol is intended. Where a procedure calls for dehydrated alcohol, alcohol absolute, or anhydrous alcohol, the *USP* monograph article Dehydrated Alcohol shall be used.

8.40. Atomic Weights

Atomic weights used in computing molecular weights and the factors in the assays and elsewhere are those established by the IUPAC Commission on Atomic Weights and Isotopic Abundances.

8.50. Blank Determinations

Where it is directed that "any necessary correction" be made by a blank determination, the determination shall be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

8.60. Concomitantly

"Concomitantly" denotes that the determinations or measurements are to be performed in immediate succession.

8.70. Desiccator

The instruction "in a desiccator" indicates use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of a suitable desiccant such as anhydrous calcium chloride, magnesium perchlorate, phosphorus pentoxide, or silica gel. See also section 8.220, *Vacuum Desiccator*.

8.80. Logarithms

Logarithms are to the base 10.

8.90. Microbial Strain

A microbial strain cited and identified by its ATCC catalog number shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

8.100. Negligible

"Negligible" indicates a quantity not exceeding 0.50 mg.

8.110. NLT/NMT

"NLT" means "not less than." "NMT" means "not more than."

8.120. Odor

"Odorless," "practically odorless," "a faint characteristic odor," and variations thereof indicate evaluation of a suitable quantity of freshly opened material after exposure to the air for 15 minutes. An odor designation is descriptive only and should not be regarded as a standard of purity for a particular lot of an article.

8.130. Percent

"Percent" used without qualification means:

- For mixtures of solids and semisolids, percent weight in weight;
- For solutions or suspensions of solids in liquids, percent weight in volume;
- For solutions of liquids in liquids, percent volume in volume;
- For solutions of gases in liquids, percent weight in volume.

For example, a 1 percent solution is prepared by dissolving 1 g of a solid or semisolid, or 1 mL of a liquid, in sufficient solvent to make 100 mL of the solution.

8.140. Percentage Concentrations

Percentage concentrations are expressed as follows:

- *Percent Weight in Weight* (w/w) is defined as the number of g of a solute in 100 g of solution.
- *Percent Weight in Volume* (w/v) is defined as number of g of a solute in 100 mL of solution.
- *Percent Volume in Volume* (v/v) is defined as the number of mL of a solute in 100 mL of solution.

8.150. Pressure

Pressure is determined by use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

8.160. Reaction Time

Reaction time is 5 minutes unless otherwise specified.

8.170. Specific Gravity

Specific gravity is the weight of a substance in air at 25° divided by the weight of an equal volume of water at the same temperature.

8.180. Temperatures

Temperatures are expressed in centigrade (Celsius) degrees, and all measurements are made at 25° unless otherwise indicated. Where moderate heat is specified, any temperature not higher than 45°(113° F) is indicated.

8.190. Time

Unless otherwise specified, rounding rules, as described in section 7.20, *Rounding Rules*, apply to any time specified.

8.200. Transfer

"Transfer" indicates a quantitative manipulation.

8.210. Vacuum

"Vacuum" denotes exposure to a pressure of less than 20 mm of mercury (2.67 kPas), unless otherwise indicated.

8.220. Vacuum Desiccator

"Vacuum desiccator" indicates a desiccator that maintains a low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury (2.67 kPas) or at the pressure designated in the individual monograph.

8.230. Water

8.230.10. Water as an Ingredient in an Official Product

As an ingredient in an official product, water meets the requirements of the appropriate water monograph in *USP* or *NF*.

8.230.20. Water in the Manufacture of Official Substances

When used in the manufacture of official substances, water may meet the requirements for drinking water as set forth in the regulations of the U.S. Environmental Protection Agency (potable water).

8.230.30. Water in a Compendial Procedure

When water is called for in a compendial procedure, the *USP* article Purified Water shall be used unless otherwise specified. Definitions for *High-Purity Water* and *Carbon Dioxide–Free Water* are provided in *Containers—Glass* ⟨660⟩. Definitions of other types of water are provided in *Water for Pharmaceutical Purposes* ⟨1231⟩.

8.240. Weights and Measures

In general, weights and measures are expressed in the International System of Units (SI) as established and revised by the *Conférence générale des poids et mesures*. For compendial purposes, the term "weight" is considered to be synonymous with "mass."

Molality is designated by the symbol *m* preceded by a number that represents the number of moles of the designated solute contained in 1 kilogram of the designated solvent.

Molarity is designated by the symbol M preceded by a number that represents the number of moles of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 liter of solution.

Normality is designated by the symbol N preceded by a number that represents the number of equivalents of the designated solute contained in an amount of the designated solvent that is sufficient to prepare 1 liter of solution.

Symbols commonly employed for SI metric units and other units are as follows:

Bq = becquerel	dL = deciliter
kBq = kilobecquerel	L = liter
MBq = megabecquerel	mL = milliliter[c]
GBq = gigabecquerel	µL = microliter
Ci = curie	Eq = gram-equivalent weight
mCi = millicurie	mEq = milliequivalent
µCi = microcurie	mol = gram-molecular weight (mole)
nCi = nanocurie	Da = dalton (relative molecular mass)
Gy = gray	mmol = millimole
mGy = milligray	Osmol = osmole
m = meter	mOsmol = milliosmole
dm = decimeter	Hz = hertz
cm = centimeter	kHz = kilohertz
mm = millimeter	MHz = megahertz
µm = micrometer (0.001mm)	V = volts
nm = nanometer[a]	MeV = million electron volts
kg = kilogram	keV = kilo-electron volt
g = gram	mV = millivolt
mg = milligram	psi = pounds per square inch
µg; mcg = microgram[b]	Pa = pascal
ng = nanogram	kPa = kilopascal
pg = pictogram	g = gravity (in centrifugation)
fg = femtogram	

[a]Previously the symbol mµ (for millimicron) was used.

[b]One milliliter (mL) is used herein as the equivalent of one cubic centimeter (cc).

[c]The symbol µg is used in the *USP* and *NF* to represent micrograms, but micrograms may be represented as "mcg" for labeling and prescribing purposes. The term "gamma," symbolized by γ, frequently is used to represent micrograms in biochemical literature.

9. PRESCRIBING AND DISPENSING

9.10 Use of Metric Units

Prescriptions for compendial articles shall be written to state the quantity and/or strength desired in metric units unless otherwise indicated in the individual monograph (see also *Units of Potency*, section 5.50.10 above). If an amount is prescribed by any other system of measurement, only an amount that is the metric equivalent of the prescribed amount shall be dispensed. Apothecary unit designations on labels and labeling shall not be used.

9.20 Changes in Volume

In the dispensing of prescription medications, slight changes in volume owing to variations in room temperatures may be disregarded.

10. PRESERVATION, PACKAGING, STORAGE, AND LABELING

10.10. Storage Under Nonspecific Conditions

If no specific directions or limitations are provided in the *Packaging and Storage* section of an individual *USP* monograph or in the labeling of an article recognized in *USP*, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Such articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Drug substances are exempt from the requirements in this paragraph.

Regardless of quantity, where no specific storage directions or limitations are provided in an individual *NF* monograph or stated in the labeling of an article recognized in *NF*, the conditions of storage and distribution shall include protection from moisture, freezing, excessive heat, and, where necessary, from light.

10.20. Containers

The container is that which holds the article and is or may be in direct contact with the article. The immediate container is that which is in direct contact with the article at all times. The closure is a part of the container.

Before being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The compendial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

10.20.10. Tamper-Evident Packaging

The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the tamper-evident packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging used by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

10.20.20. Light-Resistant Container

A light-resistant container (see *Light Transmission Test* under *Containers—Performance Testing* ⟨671⟩) protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering before dispensing.

10.20.30. Well-Closed Container

A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

10.20.40. Tight Container

A tight container protects the contents from contamination by extraneous liquids, solids, or vapors; from loss of the article; and from efflorescence, deliquescence, or evaporation under the ordinary or

customary conditions of handling, shipment, storage, and distribution; and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-Index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

[NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container used for an article when dispensed on prescription meets the requirements under *Containers—Performance Testing* ⟨671⟩.]

10.20.50. Hermetic Container

A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

10.20.60. Single-Unit Container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

10.20.70. Single-Dose Container

A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled. (See also *Containers for Injections* under *Injections* ⟨1⟩.)

10.20.80. Unit-Dose Container

A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

10.20.90. Unit-of-Use Container

A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

10.20.100. Multiple-Unit Container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

10.20.110. Multiple-Dose Container

A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only. (See also *Containers for Injections* under *Injections* ⟨1⟩).

10.20.120. Requirements under the Poison Prevention Packaging Act (PPPA)

This act (see the website, www.cpsc.gov/businfo/pppa.html) requires special packaging of most human oral prescription drugs, oral controlled drugs, certain non-oral prescription drugs, certain dietary supplements, and many over-the-counter (OTC) drug preparations in order to protect the public from personal injury or illness from misuse of these preparations (16 CFR § 1700.14).

The immediate packaging of substances regulated under the PPPA shall comply with the special packaging standards (16 CFR § 1700.15 and 16 CFR § 1700.20). The PPPA regulations for special packaging apply to all packaging types including reclosable, nonclosable, and unit-dose types.

Special packaging is not required for drugs dispensed within a hospital setting for inpatient administration. Manufacturers and packagers of bulk-packaged prescription drugs do not have to use special packaging if the drug will be repackaged by the pharmacist. PPPA-regulated prescription drugs may be dispensed in non–child-resistant packaging upon the request of the purchaser or when directed in a legitimate prescription (15 U.S.C. § 1473).

Manufacturers or packagers of PPPA-regulated OTC preparations are allowed to package one size in non–child-resistant packaging as long as popular-size, special packages are also supplied. The non–child-resistant package requires special labeling (16 CFR § 1700.5).

Various types of child-resistant packages are covered in ASTM International Standard D-3475, Standard Classification of Child-Resistant Packaging. Examples are included as an aid in the understanding and comprehension of each type of classification.

10.30. Storage Temperature and Humidity

Specific directions are stated in some monographs with respect to the temperatures and humidity at which official articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply. (See also *Pharmaceutical Stability* ⟨1150⟩.) The conditions are defined by the following terms.

10.30.10. Freezer

"Freezer" indicates a place in which the temperature is maintained thermostatically between –25° and –10° (–13° and 14°F).

10.30.20. Cold

Any temperature not exceeding 8° (46°F) is "cold." A "refrigerator" is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46°F).

10.30.30. Cool

Any temperature between 8° and 15° (46° and 59°F) is"cool." An article for which storage in a *cool place* is directed may, alternatively, be stored and distributed in a *refrigerator*, unless otherwise specified by the individual monograph.

10.30.40. Controlled Cold Temperature

"Controlled cold temperature" is defined as temperature maintained thermostatically between 2° and 8° (36° and 46° F), that allows for excursions in temperature between 0° and 15° (32° and 59° F) that may be experienced during storage, shipping, and distribution such that the allowable calculated mean kinetic temperature is not more than 8° (46° F). Transient spikes up to 25° (77° F) may be permitted if the manufacturer so instructs and provided that such spikes do not exceed 24 hours unless supported by stability data or the manufacturer instructs otherwise.

10.30.50. Room Temperature

"Room temperature" indicates the temperature prevailing in a working area.

10.30.60. Controlled Room Temperature

"Controlled room temperature" indicates a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and 30° (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40° are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Pharmaceutical Stability* ⟨1150⟩.)

An article for which storage at *controlled room temperature* is directed may, alternatively, be stored and distributed in a *cool place*, unless otherwise specified in the individual monograph or on the label.

10.30.70. Warm

Any temperature between 30° and 40° (86° and 104°F) is "warm."

10.30.80. Excessive Heat

"Excessive heat" means any temperature above 40° (104°F).

10.30.90. Protection From Freezing

Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

10.30.100. Dry Place

The term "dry place" denotes a place that does not exceed 40% average relative humidity at *Controlled Room Temperature* or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered storage in a dry place.

10.40. Labeling

The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in these compendia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the compendial requirements set forth for the articles.

10.40.10. Amount of Ingredient Per Dosage Unit

The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Official articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* ⟨698⟩. Official drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see 8.140., *Percentage Concentrations*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units. See also 5.50.10., *Units of Potency (Biological)*.

10.40.20. Use of Leading and Terminal Zeros

To help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than 1 shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

10.40.30. Labeling of Salts of Drugs

It is an established principle that official articles shall have only one official title. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids, but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

10.40.40. Labeling Vitamin-Containing Products

The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

10.40.50. Labeling Botanical-Containing Products

The label of an herb or other botanical intended for use as a dietary supplement bears the statement, "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product."

10.40.60. Labeling Parenteral And Topical Preparations

The label of a preparation intended for parenteral or topical use states the names of all added substances (see 5.20., *Added Substances, Excipients, and Ingredients* and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

10.40.70. Labeling Electrolytes

The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

10.40.80. Labeling Alcohol

The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

10.40.90. Special Capsules and Tablets

The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it shall be used.

10.40.100. Expiration Date and Beyond-Use Date

The label of an official drug product or nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/08," "Exp. June 08," or "Expires 6/08"). [NOTE—For additional information and guidance, refer to the Consumer Healthcare Products Association's *Voluntary Codes and Guidelines of the Self-Medication Industry*.]

The monographs for some preparations state how the expiration date that shall appear on the label shall be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the compendial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article shall not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to

limit the patient's use of the article based on any information supplied by the manufacturer and the *General Notices*. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution before use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) 1 year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be 1 year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturer's container, whichever is earlier, unless stability data or the manufacturer's labeling indicates otherwise.

The dispenser shall maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The plastic material used in packaging the dosage forms shall afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records shall be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

10.40.100.1. Compounded Preparations

The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, may be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see *Stability Criteria and Beyond-Use Dating* under *Stability of Compounded Preparations* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

10.50. Guidelines for Packaging and Storage Statements in *USP–NF* Monographs

In order to provide users of the *USP* and *NF* with proper guidance on how to package and store official articles, every monograph in the *USP* and *NF* shall have a packaging and storage specification.

For the packaging portion of the statement, the choice of containers is given in this section 10, *Preservation, Packaging, Storage, and Labeling*, and includes *Light-Resistant Container*, *Well-Closed Container*, *Tight Container*, *Hermetic Container*, *Single-Unit Container*, *Single-Dose Container*, *Unit-Dose Container*, and *Unit-of-Use Container*. For most preparations, the choice is determined by the container in which it shall be dispensed (e.g., tight, well-closed, hermetic, unit-of-use, etc.). For drug substances, the choice would appear to be tight, well-closed, or, where needed, a light-resistant container. For excipients, given their typical nature as large-volume commodity items, with containers ranging from drums to tank cars, a well-closed container is an appropriate default. Therefore, in the absence of data indicating a need for a more protective class of container, the phrase "Preserve in well-closed containers" should be used as a default for excipients.. *USP32*

Exhibit 56

2006 WL 166452
Only the Westlaw citation is currently available.
NOT FOR PUBLICATION
United States District Court, D. New Jersey.

Jeff PLAYER, et al., Plaintiffs,
v.
MOTIVA ENTERPRISES LLC, a successor in interest to Star Enterprises, Defendant.

No. Civ. 02–3216(RBK).
Jan. 20, 2006.

Attorneys and Law Firms

Keith A. McKenna, McKenna, Mulcahy & McKenna, Montclair, NJ, for Plaintiffs.

Jeffrey W. Moryan, Connell Foley LLP, Roseland, NJ, for Defendant.

OPINION

KUGLER, United States District Judge:

***1** This matter comes before the Court upon motions by Defendant Motiva Enterprises, LLC, ("Defendant" or "Motiva") for summary judgment of the claims of Plaintiffs Jeff Player, et al. ("Plaintiffs"), and to exclude Plaintiffs' experts Michael Gochfeld, M.D., Ph.D. ("Gochfeld"), R. Brian Ellwood, Ph.D. ("Ellwood"), Bruce M. Gallo ("Gallo"), and Daniel McDonald ("McDonald"). For the reasons set forth below, Defendant's motions will be granted in part and denied in part.

I. Background [1]

This environmental contamination suit is brought by the current and former owners of twenty-seven parcels of residential property located in the Spring Hollow Subdivision in Gloucester Township, New Jersey. [2] Plaintiffs allege that emissions from Defendant's nearby Texaco gasoline service station contaminated their property and the Kirkwood Cohansey Aquifer, the underground water source for their potable wells.

Contamination of the aquifer was first detected on April 5, 2000, when significant concentrations of the gasoline-related compound methyl tertiary butyl ether ("MTBE") was discovered in a drinking fountain at Camden County Community College. New Jersey Consumers Water Company ("Consumers"), the entity responsible for providing water to the college, conducted sampling of some of its wells and discovered significant amounts of gasoline-related compounds in municipal supply well number 8 ("CW–8"). Consumers took the well offline on April 10.

While investigating the contamination, the New Jersey Department of Environmental Protection ("NJDEP") detected a discharge of volatile organic compounds ("VOCs") from Defendant's service station, located at 585 Berlin Cross Keys Road ("Motiva site" or "contamination site"). [3] The NJDEP issued a Field Directive on April 12, 2000, requiring Motiva to investigate the source and extent of the discharge, to implement an interim treatment system, and to submit a remedial action work plan to the NJDEP. Defendant installed an interim recovery system and twenty-five monitoring and recovery wells between April and June 2000.

The NJDEP issued a second directive on May 5, 2000, ordering Defendant to cease gasoline retail operations and provide treatment or an alternate source of water to replace CW–8. Defendant replaced the interim system with a permanent ground water recovery and treatment system in June 2000, and installed forty-one additional monitoring wells from June 2000 to present. As further required by the NJDEP, Defendant regularly sampled potable wells located on approximately forty residential properties in the vicinity of the Motiva site. Defendant detected small amounts of MTBE in thirteen of the residential wells it sampled. [4]

Per the NJDEP directive, Motiva submitted a Remedial Investigation Work Plan/Remedial Investigation report on July 2000 and a Remedial Action Workplan ("RAW") on November 14, 2000. In its RAW, Defendant requested permission to cease sampling of the residential wells, contending that the MTBE detected in those wells could not have come from the Motiva site since the wells are located upgradient [5] or sidegradient from the site, and no emissions were detected in most of the monitoring wells between the Motiva site and the potable wells. [6] Motiva also claimed that recent literature indicated that traces of MTBE in groundwater could likely result from "non-point sources." (March 2001 Directive at 2.)

***2** Plaintiffs' expert, R. Brian Ellwood, Ph.D ("Ellwood"), submitted a response to the RAW on January 17, 2001. In his report, Ellwood notes that as of January 17, 2001, "[c]ontrol of contamination at depth beneath the site, control of offsite contamination, and possibly control of contamination at the northern site boundary, has not been established." (Preliminary Report Sicklerville Road Groundwater Contamination ("Ellwood Report"), McKenna Cert. in Opp. to Def.'s Mot. Summ. J., filed Oct. 12, 2005 ("McKenna Cert."), Ex. F, at 2.) Ellwood also offered possible theories to demonstrate the plausibility of Defendant's responsibility for the MTBE in spite of Motiva's arguments to the contrary.

The NJDEP ultimately rejected Defendant's request to cease sampling of the residential wells in its March 2001 Directive on the basis that "there is insufficient evidence for Equiva to conclude that the MTBE detected in the 13 potable wells in the area did not originate from the Cross Keys Texaco site" and "that regardless of the source of the MTBE in these wells, which is obviously debatable, ongoing sampling of these wells is required *primarily due to their proximity to the site."* (March 2001 Directive at 2) (emphasis in original).

Also in the March 2001 Directive, the NJDEP approved a Classification Exemption Area ("CEA") for the site that excluded all but 1/10 of an acre of 583 Berlin Cross Keys Road (the Wallace Property). The CEA establishes the boundaries of a ground water plume where VOCs exceed the GWQS. [7]

Through summer 2004, the NJDEP regularly reduced the testing requirements. By August 18, 2003, the NJDEP required only:

> annual sampling of the wells at 4, 7, 11, 13 and 14 Donna Marie Court; 2, 4, 6, and 8 Latham Way; 12 and 20 Spring Hollow Drive, and; 937 and 948 Sicklerville Road. For all the sampling events of the aforementioned potable wells conducted April 2002, the Department notes that all wells continue to exhibit no gasoline related contamination in excess of the Department's Drinking Water Quality Standards.

(NJDEP Directive, Aug. 18, 2003, McKenna Cert., Ex. D.)

The NJDEP approved shut down of the recovery and treatment system on April 30, 2004. (NJDEP Correspondence, Aug. 9, 2004, Mairo Cert., Ex. S., at 2.) Finally, on August 9, 2004, the NJDEP determined that "Defendant's Remedial Action Progress Reports "meet the conditions of the March 21, 2001 Remedial Action Workplan (RAW) approval. Shell Oil Products U.S. (Shell OPUS) is, therefore, in compliance with N.J.A.C. 7:14B–6." (Aug. 9, 2004, NJDEP Correspondence, Mairo Cert., Ex. S., at 1.)

B. The Residential Properties

Plaintiffs own twenty-seven respective residential properties near Defendant's gasoline station. [8] Twenty-six of the twenty-seven properties-all but 583 Berlin Cross Keys Road ("the Wallace property")-contain potable wells located in the Kirkwood Cohansey Aquifer. Because Plaintiffs' properties are north/northeast of the contamination site, (Undisputed Facts ¶ 38), they are considered upgradient or sidegradient of the contamination site, depending on whether CW–8 is pumping. [9]

***3** Consistent with the requirements of the NJDEP directives, Defendant tested the Plaintiffs' residential wells for six gasoline-related compounds: benzene, toluene, ethylbenzene, xylenes, MTBE, and TBA. No testing detected any gasoline-related compound on eighteen of the properties. [10] Detection of compounds on the remaining eight properties was as follows:

- A single detection of 0.79 ppb toluene and ten detections of MTBE (highest at 15.5 ppb) at 4 Latham Way,
- Three detections of MTBE (highest at 0.76 ppb) at 14 Donna Marie Court,
- Three detections of MTBE (highest at 1.4 ppb) at 6 Latham Way,
- A single detection of 1.4 ppb toluene at 850 Sicklerville Road,

- A single detection of 0.4 ppb MTBE at 4 Donna Marie Court,
- A single detection of 0.3 ppb MTBE at 12 Donna Marie Court,
- A single detection of 1.2 ppb MTBE at 8 Latham Way, and
- A single detection of 0.3 ppb MTBE at 20 Spring Hollow Road.

The GWQS for toluene is 1,000 ppb and the GWQS for MTBE is 70 ppb. No gasoline-related compound was detected on any Plaintiff's property after April 2001.

According to the Certification of Julian Davies, a Project Manager for EnviroTrac, Ltd., an environmental consulting firm retained by Defendant to remediate the Motiva site, the NJDEP never restricted the consumption of water from Plaintiffs' potable wells, and never required Defendant to treat the water, provide Plaintiffs with an alternate source of water, or collect soil samples from the residential properties. [11] (Julian Davies Cert., Mairo Cert., Ex. R, at 2.)

Since the fact of the contamination became known, several Plaintiffs have sold their property. Maria and John Wallace sold 583 Berlin Cross Keys Road for $350,000.00 in September 2001, Plaintiffs Thomas and Tina Stankiewicz sold 9 Spring Hollow Drive in July 2002 for $143,000.00, Barbara Tanner sold 17 Spring Hollow Drive for $134,000.000 in February 2002, Daniel and Maria Rodriguez sold 18 Spring Hollow Drive for $138,000.00 in July 2003, David Lodi sold 5 Donna Marie Court for $104,000.00 in September 2001, 13 Donna Marie Court was sold for $109,900.00 in July 2000, and 19 Spring Hollow Drive was sold for $133,900.00 in May 2001.

Defendant filed motions for summary judgment and to exclude experts on June 24, 2005, after requesting and receiving permission from this Court to extend by one week the date for the filing of dispositive and *in limine* motions. Briefs in opposition were due July 22, 2005, however, Plaintiffs instead filed an untimely request for an extension on August 2, 2005, and a second request on September 6, 2005, moving the deadline to September 30, 2005. On October 5, 2005, Plaintiffs filed another untimely request for an extension, and ultimately did not submit a complete Opposition until October 14, 2005. Nevertheless, because a district court should not grant a motion for summary judgment without examining the merits, *Stackhouse v. Mazurkiewicz*, 951 F.2d 29, 30 (3d Cir.1991) (citing *Anchorage Assoc. v. Virgin Islands Bd. of Tax Rev.*, 922 F.2d 168 (3d Cir.1990)), this Court will exercise its discretion to consider Plaintiffs' Opposition, even though it is untimely. Local Civ. R. 7.1(d)(5).

II. Standard

***4** Summary judgment is appropriate where the Court is satisfied that "there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 330, 106 S.Ct. 2548, 91 L.Ed.2d 265 (1986). A genuine issue of material fact exists only if "the evidence is such that a reasonable jury could find for the nonmoving party." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986).

The burden of establishing the nonexistence of a "genuine issue" is on the party moving for summary judgment. *Celotex*, 477 U.S. at 330. The moving party may satisfy this burden by either (1) submitting affirmative evidence that negates an essential element of the nonmoving party's claim; or (2) demonstrating to the Court that the nonmoving party's evidence is insufficient to establish an essential element of the nonmoving party's case. *Id.* at 331.

Once the moving party satisfies this initial burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e). To do so, the nonmoving party must "do more than simply show that there is some metaphysical doubt as to material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586, 106 S.Ct. 1348, 89 L.Ed.2d 538 (1986). Rather, to survive summary judgment, the nonmoving party must "make a showing sufficient to establish the existence of [every] element essential to that party's case, and on which that party will bear the burden of proof at trial." *Serbin*, 96 F.3d at 69 n. 2 (quoting *Celotex*, 477 U.S. at 322); *Heffron v. Adamar of N.J., Inc.*, 270 F.Supp.2d 562, 568–69 (D.N.J.2003). "If the non-movant's evidence on any essential element of the claims asserted is merely 'colorable' or is 'not significantly probative,' the court must enter summary judgment in favor of the moving party."

Heffron, 270 F.Supp.2d at 69 (citing *Anderson,* 477 U.S. at 249–50).

III. Motion to Exclude Expert Daniel McDonald

Defendant moves to exclude the testimony of Plaintiffs' expert Daniel McDonald ("McDonald") on the grounds that he is unqualified and his report is unreliable. [12] Admissibility of expert testimony is governed by Federal Rule of Evidence 702 and the United States Supreme Court's decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). [13] In the Third Circuit, the admissibility of expert testimony is contingent on the "qualifications" of the expert and the "reliability" of his methodology. *In re Paoli R.R. Yard PCB Litig.,* 35 F.3d 717 (3d Cir.1994) (interpreting *Daubert*); *see also Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000).

A. *In Limine* Hearing

In certain instances, courts are obligated to provide *in limine* hearings before applying *Daubert* to exclude expert testimony. *Padillas v. Stork–Gamco, Inc.,* 186 F.3d 412 (3d Cir.1999). A hearing is required, for example, where the court excludes an expert's conclusions on the grounds that they are "insufficiently explained and the reasons and foundations for them inadequately and perhaps confusingly explicated." *Id.* In other words, where a report is "conclusory and did not adequately explain the basis for [the expert's] opinion or the methodology employed in reaching his conclusions," the "plaintiff needs an 'opportunity to be heard' on the critical issues of scientific reliability and validity." *Oddi,* 234 F.3d 136, 152 (3d Cir.2000) (holding that the district court did not err "in granting summary judgment here without an *in limine* hearing") (quoting *Padillas,* 186 F.3d at 417). Where the evidentiary record is substantial, however, or the court has before it the information necessary to determine that the expert lacks "good grounds" for his conclusions, an *in limine* hearing may be unnecessary. *Id.* at 153.

***5** The evidence before this Court clearly establishes the process by which McDonald "arrived at his conclusions," *Oddi,* 234 F.3d at 152, and McDonald's report and deposition details the methodology underlying his determinations. As discussed below, this Court will exclude McDonald's testimony on the grounds that his analysis and methodology are baseless and inconclusive, not because his report is insufficiently explained. Additionally, Defendant's motion for summary judgment alerted Plaintiffs to the *Daubert* challenge, yet Plaintiffs neither requested a hearing nor offered any affidavit or evidence in support of McDonald. Accordingly, an *in limine* hearing is unnecessary.

B. Qualifications

The Third Circuit instructs courts to "liberally" evaluate an expert's qualifications. *Oddi v. Ford Motor Co.,* 234 F.3d 136, 145 (3d Cir.2000). In particular, the Circuit has "eschewed overly rigorous requirements of expertise and [has] been satisfied with more generalized qualifications." *In re Paoli,* 35 F.3d at 741 (citing *Hammond v. International Harvester Co.,* 691 F.2d 646, 652–53 (3d Cir.1982) and *Knight v. Otis Elevator Co.,* 596 F.2d 84, 87–88 (3d Cir.1979)). This liberal treatment extends to the expert's substantive qualifications as well as his formal qualifications. *Id.*

Nevertheless, the Third Circuit has "also set a floor with respect to an expert witness's qualifications." *Elcock v. Kmart Corp.,* 233 F.3d 734, 742 (3d Cir.2000). To demonstrate when an expert would not be qualified under Rule 702, the *Elcock* Court offered the pre-*Daubert* case, *Aloe Coal Co. v. Clark Equip. Co.,* 816 F.2d 110 (3d Cir.1987), which held a tractor salesperson unqualified to testify as an expert about the cause of a tractor fire. *Elcock,* 233 F.3d at 742 (citing *Aloe Coal,* 816 F.2d 110).

In *Elcock* itself, the Court determined with "misgivings" that the district court had not abused its discretion by concluding that a psychologist with experience in obtaining employment for disabled individuals was qualified to testify to the possibility for vocational rehabilitation of the injured plaintiff. However, the Court acknowledged that it also would have upheld a decision to exclude the expert since "he seems most qualified to testify on a micro-level regarding the ability of a disabled individual to return to a specific job; he does not appear particularly qualified to testify on the macro-level regarding the number of jobs in the national or local economy that the disabled individual is able to perform." [14] *Elcock,* 233 F.3d at 744. Taken together, *Elcock* and *Aloe Coal* indicate that where a proposed expert's area of experience is

adjacent to, but not actually encompassing, the subject matter of his testimony, he may be deemed unqualified.

McDonald has worked as a licensed appraiser in New Jersey for approximately twenty-two years. Defendant argues that McDonald is nevertheless unqualified to testify to the diminution in value of Plaintiffs' properties because McDonald has no experience in appraising contaminated property. Defendant notes that McDonald has never appraised property allegedly contaminated by emissions from a gasoline station and has never acted as an expert in a situation involving contamination of the groundwater or allegations of a leaking underground storage tank. (Daniel McDonald Dep. ("McDonald Dep."), Mairo Cert. in Supp. Def.'s Mot. to Exclude Plaintiffs' Expert Daniel McDonald, Ex. C, at 23–24.) Defendant also points out that McDonald did not entirely understand the Ellwood and Gallo reports upon which he relied, including the charts indicating the presence and degree of contaminating agents on the property. (McDonald Dep. at 55–56.)

***6** This case lies squarely between *Aloe Coal* and *Elcock.* Although McDonald is an experienced appraiser, no evidence indicates that he has any experience appraising contaminated properties or is qualified to value the effects of stigma on property values. Just as a psychologist experienced in assisting individuals to find work may be unqualified to testify about the general availability of jobs in the economy, an individual able to appraise an uncontaminated property may have no grounds for appreciating the devaluation of the same property under unique conditions of contamination or stigma. Because nothing in McDonald's experience indicates knowledge or expertise in issues of contamination, he is unqualified to testify to the loss of value to Plaintiffs' properties arising from the alleged contamination.

C. Reliability

Because expert testimony has the potential to bear considerable weight with a jury, the district court functions as a gatekeeper responsible for assuring "that the scientific methodology upon which the expert opinion is founded is reliable" and that "the expert's conclusion is based on good grounds." *In re Paoli,* 35 F.3d at 732–33. To ascertain "reliability," the court must examine a number of factors, both those established in *Daubert* and those previously enumerated by the Third Circuit in *United States v. Downing,* 753 F.2d 1224 (3d Cir.1985). *Oddi,* 234 F.3d 145 (citing *Paoli II,* 35 F.3d at 742). In particular, the court must consider:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subjected to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Paoli II, 35 F.3d at 742 n. 8; *see also Elcock,* 233 F.3d at 746 (noting that "each factor need not be applied in every case"). The party wishing to introduce the testimony bears the burden of establishing "by a preponderance of the evidence that their opinions are reliable." *Paoli,* 35 F.3d at 744.

Of course, an expert's opinion need not be "perfect," and judges may not substitute their opinions for those of an expert. *Paoli,* 35 F.3d at 744; *see also Crowley v. Chait,* 322 F.Supp.2d 530, 536 (D.N.J.2004). However, courts also need not admit mere conclusions or "opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Magistrini v. One Hour Martinizing Dry Cleaning,* 180 F.Supp.2d 584, 608 (D.N.J.2002) (quoting *General Elec. Co. v. Joiner,* 522 U.S. 136, 145–46, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)).

***7** Mere assumptions, without causal evidence or methodological analysis may be inadmissible. *In re TMI Litig.,* 193 F.3d 613, 667–68 (3d Cir.1999). Conclusions based only on the expert's experience, *Oddi,* 234 F.3d at 140–41, and testimony founded on methods that are not

generally accepted or lack testable hypotheses may also fail to surmount the *Daubert* standard, *Elcock,* 233 F.3d at 746. Furthermore, conclusions based on analogies that are too dissimilar to the subject of the testimony may also merit exclusion. *General Elec.,* 522 U.S. at 144 (rejecting expert testimony that plaintiff's cancer was due to exposure to PCBs when the testimony was based on animal studies of infant mice that had developed cancer after exposure to PCBs).

In response to Defendant's motion to exclude McDonald's testimony, Plaintiffs argue that "Mr. McDonald's opinions are based upon credible facts, NJDEP records, the reports of Plaintiffs' liability experts and individual appraisal reports prepared for each residential property." (Pl.s' Opp. Def.'s Mot. Summ. J. ("Opp."), filed Oct. 12, 2005, at 30.) However, McDonald testified in his deposition that he relied only on the Gallo and Ellwood Reports, and he specifically testifies that he did *not* "review any correspondence from the NJDEP related to this site." (McDonald Dep. at 15.) [15]

In spite of Plaintiffs' arguments to the contrary, this Court cannot avoid the conclusion that McDonald's methodology is entirely unreliable. In his report, McDonald determines that the value of Plaintiffs' properties with no evidence of contamination should be discounted 35% percent and property with onsite contamination should be discounted by 66%. (McDonald Report ("McDonald Report"), Mairo Cert. in Support of Def.'s Mot. Exclude Pl.s' Expert Daniel McDonald, Ex. B., at 31, 33.) McDonald reached the 35% and 66% figures without discussing, or even recognizing, the extent to which the property was actually contaminated. As demonstrated by his ignorance of the "ND"/Not Detected signifier in the Gallo and Ellwood Reports, McDonald did not know how to read the charts denoting the levels of contamination. (McDonald Dep. at 56.) Nor had McDonald ever conducted any physical inspection of or visit to the properties prior to writing the report. [16] (McDonald Dep. at 15–16.)

Furthermore, to quantify the stigma attached to Plaintiffs' properties, McDonald relies upon a highly misleading analogy with a site of profoundly contaminated residential properties in Dover Township. (McDonald Report at 27.) Specifically, McDonald compares Plaintiffs' properties with "an area of Dover Township that had ground water contamination from Union Carbide and ... Ciba Geigy that resulted in what was commonly known as a cancer cluster among children," meaning "an inordinate number of children with cancer." (McDonald Dep. at 158–59.) McDonald selected the Dover site not because of its comparability, but because McDonald "didn't know of any other cases that, where the data was as readily available." (McDonald Dep. at 159.)

***8** Employing the Dover analogy, McDonald determined that the property in the Dover site is in the final stages of recovery and continues to suffer a stigma loss of 13%. Because McDonald considered Plaintiffs' properties in the early stages of recovery, McDonald determined that they must bear a stigma discount of at least two or three times that of the Dover site, resulting in a discount of 35%. [17] However, the severity of the contamination and resulting illness among Dover residents undercuts any grounds for comparison with Plaintiffs' properties where there were few detections of contaminants and no reported physiological effects.

The methodology employed to reach the 66% figure is equally unreliable. To assess the value of properties with some evidence of contamination, McDonald sent an email to thirteen financial lenders to determine whether they would "lend on a property that has known contamination, or the stigma of contamination, to the ground water." (McDonald Report at 32.) Of the thirteen lenders, six replied. One of those refused to comment, and one said that it would loan given certain circumstances. The other four lenders stated that they would not lend on a property that is contaminated, but the content of their brief responses suggested that they understood the email hypothetical to denote property that was actually contaminated and out of compliance with state requirements. [18]

From the results of the email test, McDonald concludes that there would be no buyers other than those who could pay cash. [19] McDonald then assessed the discount in value given cash-only buyers, extrapolating from this a discount of 66%. (McDonald Report at 33.) However, the reliability of the 66% figure is entirely invalidated by the overemphasis placed on the four responses to the email hypothetical, the misleading implication in the email hypothetical, suggesting a much greater contamination of the property than actually present, and the unclear calculations and assumptions underlying McDonald's arrival at 66%.

Ultimately, McDonald's report does not fulfil any of the reliability factors. His method is untestable and arbitrary, without a generally accepted, established, or peer reviewed methodology, and his evaluation was conducted without any

real standards. Because McDonald is unqualified and his evaluation is unreliable, Defendant's motion *in limine* to exclude his testimony will be granted.

IV. Plaintiffs' Claims

A. Negligence and Gross Negligence

To surmount a motion for summary judgment of a negligence claim, Plaintiffs must provide evidence such that a reasonable jury could find "breach of a duty of care and actual damages sustained as a proximate cause of the breach." *Muise v. GPU, Inc.,* 371 N.J.Super. 13, 35, 851 A.2d 799 (App.Div.2004) (citing *Weinberg v. Dinger,* 106 N.J. 469, 484, 524 A.2d 366 (1987)); *Nappe v. Anschelewitz, Barr, Ansell & Bonello,* 97 N.J. 37, 45, 477 A.2d 1224 (1984) ("[T]he plaintiff must show a breach of duty and resulting damage to prevail in a negligence action."). Motiva argues that Plaintiffs have failed to establish damages and causation and requests summary judgment of Plaintiffs' gross negligence claim on the same basis. [20]

***9** The absence of an injury will preclude a negligence claim, even where a clear breach of duty is present. *Rocci v. MacDonald–Cartier,* 323 N.J.Super. 18, 24–25, 731 A.2d 1205 (App.Div.1999) (affirming summary judgment for insufficient evidence of damages in defamation case and noting that "a plaintiff must present proof of a material question of fact as to both liability and damages") (citing *Norwood Easthill Assoc. v. Norwood Easthill Watch,* 222 N.J.Super. 378, 384, 536 A.2d 1317 (App.Div.1988) (affirming summary judgment of malicious interference claim on basis that "plaintiff has suffered no injury or damage")). At the summary judgment stage, Plaintiffs must provide actual evidence of injury and cannot simply rely upon "unsubstantiated allegations." *Trap Rock Indus., Inc. v. Local 825,* 982 F.2d 884, 890 (3d Cir.1992) (reversing district court's denial of summary judgment). Just as "a residential customer not in residence during a power loss, or a commercial customer whose store was closed, might have no damages except the inconvenience of resetting clocks," *Muise,* 371 N.J.Super. at 49, 851 A.2d 799, the release of contaminants into the groundwater aquifer does not itself generate damages, unless Plaintiffs can show that they suffered harm.

Plaintiffs concede that they "have not presented and will not present claims for the present manifested bodily injury." (Undisputed Facts ¶ 67.) However, they argue that they have adequately established damages for medical monitoring and property damage. They do not address their claim for emotional distress. [21]

1. Medical Monitoring

Damages for medical monitoring are appropriate where a plaintiff exhibits no physical injury, but nevertheless requires medical testing as a proximate result of a defendant's negligent conduct. *Ayers v. Jackson Twp.,* 106 N.J. 557, 600, 525 A.2d 287 (1987). The risk of injury need not be quantified to merit medical surveillance damages; however, the plaintiff must establish that the risk of serious disease is "significant." *Id.* at 599–600, 525 A.2d 287; *Campo v. Tama,* 133 N.J. 123, 131, 627 A.2d 135 (1993) (awarding medical monitoring damages to a plaintiff with a "fifty-to seventy-five-percent chance of suffering a recurrence of cancer" due to the delay resulting from defendant doctor's malpractice). In the case of toxic exposure, "medical-surveillance damages may be awarded only if a plaintiff reasonably shows that medical surveillance is required because the exposure caused a distinctive increased risk of future injury." *Theer v. Philip Carey Co.,* 133 N.J. 610, 627, 628 A.2d 724 (1993). Such damages are "not available for plaintiffs who have not experienced direct and hence discrete exposure to a toxic substance and who have not suffered an injury or condition resulting from that exposure." *Id.* at 628, 628 A.2d 724.

Low level contamination, "that is, contamination below the minimum level set by DEP for water remediation," typically is insufficient to establish injurious toxic exposure. *Muralo Co., Inc. v. Employers Ins. of Wausau,* 334 N.J.Super. 282, 290–291, 759 A.2d 348 (App.Div.2000) ("[S]ince it is clear that no untreated groundwater is ever entirely pure, we are satisfied that DEP standards are the most reliable guide for determining whether contamination causing damage ... has occurred."). Here, contaminants have been detected in only eight of Plaintiffs' wells, and no detection has been even close to the GWQS. The NJDEP never restricted Plaintiffs' use of water from their potable wells, nor required Defendant to treat Plaintiffs' wells or to provide Plaintiffs with an alternate water source.

***10** Plaintiffs rely on the testimony of Dr. Michael Gochfeld, Ph.D. ("Gochfeld"), to establish the significant health risks

and necessity of medical surveillance following from the alleged contamination of Plaintiffs' property. However, nothing in Gochfeld's report concludes that the individual Plaintiffs themselves require medical monitoring under the circumstances. Rather, Gochfeld's report creates a medical monitoring program for a hypothetical target population without taking into consideration the actual exposure of any plaintiff.[22] (Gochfeld Dep. at 26–29.) Gochfeld prepared his report under the assumption that "there were known or actual or potential exposure to a variety of constituents of gasoline." (Gochfeld Dep. at 12.) He states in deposition that he had "no specific factual knowledge of the actual exposures in this case," and he confirms that he has never examined the individual Plaintiffs. (Gochfeld Dep. at 10, 29.)

Gochfeld himself notes that "[w]hether a person exposed to MTBE requires medical monitoring depends in large measure on the level of exposure and the time over which it occurred" and notes that "clearly people that are exposed to MTBE casually would not require one." (Gochfeld Dep. at 24.) Furthermore, Gochfeld stated that he "probably would not" recommend medical monitoring for the minor and often single detections of MTBE on Plaintiffs' properties.[23] (Gochfeld Dep. at 46–50.) Consequently, Gochfeld's report does not establish that Plaintiffs require medical monitoring.

Plaintiffs also appear to argue that their wells may have been more contaminated prior to the initiation of Defendant's testing in July 2000. (Opp. at 20.) However, Plaintiffs provide no evidence suggesting that such exposure actually occurred or that any exposure prior to July 2000 was more than minimal. Plaintiffs also argue for the first time in their Opposition that they may have ingested water from contaminated sources besides the potable wells on their property. (Opp. at 20.) However, Plaintiffs offer no evidence that any Plaintiff actually consumed water from CW–8. Without any evidence supporting their theories, Plaintiffs cannot establish a claim for medical monitoring sufficient to survive summary judgment.

Because Plaintiffs have provided no evidence of a "distinctive increased risk of future injury" from the exposure, Plaintiffs are not entitled to damages for medical monitoring.

2. Property Damage

Defendant requests summary judgment of Plaintiffs' claims of property damage on the grounds that the contamination caused no actual damage to Plaintiffs' properties.[24] Instead of claiming that their property was physically harmed, Plaintiffs contend that the news of the contamination stigmatized their property, reducing its value in the minds of potential buyers.

In support of their claim for stigma damages, Plaintiffs offer the expert testimony of Daniel McDonald. However, as discussed previously, McDonald's testimony must be excluded as unreliable. Plaintiffs also argue that the testimony of individual Plaintiffs establishes a stigma discount to their property:

> ***11** Plaintiff Marie Wallace has submitted sworn Interrogatory statements documenting a $150,000.00 loss on the sale of her property. See Exhibit 0 to McKenna Certification. Other Plaintiffs have similarly provided certified answers to Interrogatories and Deposition testimony as to the loss in value through sales transactions, which occurred from the discharge. See Exhibit N–R to the McKenna Certification.

(Opp. at 20–21.)

This evidence fails to establish an injury. Exhibits N–R consist of contracts for sale and unexecuted contracts for sale of three of Plaintiffs' properties, including the Wallace property, leaving it to the Court's imagination to ascertain how these contracts demonstrate a loss in value. Wallace's testimony also fails to establish a stigma injury to the property.

Specifically, Wallace claims that she received a verbal offer for her asking price of $500,000.00 from a man named "Amin," whose last name she cannot recall. (Marie Wallace Dep., McKenna Cert., Ex. 0, M.) Wallace claims that he reneged from the agreement after she told him about the release, however, the alleged offeror never gave Wallace the offer in writing and she has no evidence of the offer or "Amin's" motive for withdrawing, aside from her own testimony. Consequently, even construing this evidence in the light most favorable to Plaintiffs, no reasonable jury could find that Plaintiffs' properties were stigmatized on the basis of this evidence alone.

3. Emotional Distress

Defendant also moves for summary judgment of Plaintiffs' claim for emotional distress. Plaintiffs do not respond to this argument in their Opposition, and Defendant is entitled to summary judgment of Plaintiffs' emotional distress claim for Plaintiffs' failure to present evidence of significant distress or physical injury.

A claim for emotional distress cannot succeed absent evidence of physical injury or "severe and substantial" emotional distress, even where a person has a reasonable concern of an enhanced risk of future disease. *Ironbound Health Rights Advisory Com'n v. Diamond Shamrock Chem. Co.,* 243 N.J.Super. 170, 174–75, 578 A.2d 1248 (App.Div.1990) (noting that "[i]n the absence of physical injury, damages are allowed where the resultant emotional distress is severe and substantial" and listing cases). Without some physical injury, mere exposure to toxic chemicals does not give rise to a claim for emotional distress damages. *Id.* (holding plaintiffs unable to sustain emotional distress claim for exposure to chemicals manufactured at plant near their residences); *see also* *Mauro v. Raymark Indus., Inc.,* 116 N.J. 126, 137, 561 A.2d 257 (1989); *Troum v. Newark Beth Israel Med. Ctr.,* 338 N.J.Super. 1, 17, 768 A.2d 177 (App.Div.2001). Because Plaintiffs provided no evidence of significant emotional distress or physical injury, Defendant's motion for summary judgment will be granted.

B. Trespass

Defendant moves for summary judgment of Plaintiffs' claim for trespass. Plaintiffs argue that Defendant's "intentional refusal" to remove the contamination from their property and failure to install remediation equipment amounts to an intentional trespass.[25] (Opp. at 25.)

***12** The Restatement (Second) of Torts defines intentional trespass as:

> One who intentionally and without a consensual or other privilege
>
> (a) enters land in possession of another or any part thereof or causes a thing or third person so to do, or
>
> (b) remains thereon, or
>
> (c) permits to remain thereon a thing which the actor or his predecessor in legal interest brought thereon in the manner stated in §§ 160 and 161, is liable as a trespasser to the other irrespective of whether harm is thereby caused to any of his legally protected interests.

Rest. (2d) Torts § 158.

As Defendant argues, New Jersey has moved away from "such common law claims as trespass and nuisance" in environmental pollution cases. *Mayor and Council of Borough of Rockaway v. Klockner & Klockner,* 811 F.Supp. 1039, 1053 (D.N.J.1993); *Kenney v. Scientific, Inc.,* 204 N.J.Super. 228, 256, 497 A.2d 1310 (1985) ("There is no need for us ... to torture old remedies to fit factual patterns not contemplated when those remedies were fashioned."). Regardless of the continuing viability of trespass claims in the environmental context, however, Plaintiffs have failed to come forward with any evidence supporting their claim and cannot survive summary judgment.

Plaintiffs note that they are "not arguing that Defendants intentionally caused the contamination of their property," but rather are claiming that "defendants have repeatedly refused to perform the horizontal and vertical delineation of the soil and groundwater contamination in the area of the residential properties." (Opp. at 25.) However, no evidence suggests that such measures were necessary to remove contaminants from Plaintiffs' properties. Rather, the record indicates that Defendant consistently complied with NJDEP requirements, including the installation and maintenance of a groundwater recovery system to rehabilitate the aquifer, and the NJDEP never required Defendant to install any sort of remediation equipment on any of the residences. Given that there has been no detection of a gasoline-related contaminant in any Plaintiff's potable well since April 2001, the argument that Defendant permitted contamination to remain on Plaintiffs' properties lacks any viable evidentiary foundation. Defendant's motion for summary judgment of Plaintiffs' trespass claim will be granted.

C. Strict Liability

Plaintiffs originally claimed a cause of action for strict liability under the theory that the handling, storage, or use of gasoline constitutes an abnormally dangerous activity. However, Plaintiffs voluntarily dismissed this claim in their Opposition. (Pl.'s Opp. at 3.) Accordingly, the Court will not address the merits of Plaintiffs' strict liability claim.

D. Environmental Statutes

1. New Jersey Environmental Rights Act

Plaintiffs allege a right to recover under the New Jersey Environmental Rights Act ("ERA"), N.J.S.A. 2A:35A–1 *et seq.* Defendant requests summary judgment on the grounds that Plaintiffs have not satisfied the ERA's notice provision, N.J.S.A. 2A:35A–11, and that an ERA claim is not actionable where the NJDEP has acted to institute and oversee remediation of the contamination.

***13** Section 4(a) of the ERA, permits "any person" to "maintain an action in a court of competent jurisdiction against any other person to enforce, or to restrain the violation of, any statute, regulation or ordinance which is designed to prevent or minimize pollution, impairment or destruction of the environment." N.J.S.A. 2A:35A–4(a). Although the ERA itself does not create substantive rights, it confers standing on private persons to enforce other environmental statutes, including the New Jersey Spill Compensation and Control Act ("Spill Act"). *Rockaway,* 811 F.Supp. at 1054; *Allied Corp. v. Frola,* 701 F.Supp. 1084, 1091 (D.N.J.1988).

The NJDEP is "entrusted initially with the right to determine the primary course of action to be taken." *Howell Township v. Waste Disposal, Inc.,* 207 N.J.Super. 80, 95, 504 A.2d 19 (App.Div.1986) ("In order to be effective, [the NJDEP] must normally be free to determine what solution will best resolve a problem on a state or regional basis given its expertise and ability to view those problems and solutions broadly."). Consequently, the right of private parties to sue under the EPA is "an alternative to inaction by the government which retains primary prosecutorial responsibility." *Superior Air Prod. Co. v. NL Indus., Inc.,* 216 N.J.Super. 46, 58, 522 A.2d 1025 (App.Div.1987); *Rockaway,* 811 F.Supp. at 1054 ("[T]he primary goal of the ERA is to limit lawsuits by private litigants to those instances where the government has not acted.").

A private ERA suit may be permitted even in the absence of complete government inaction if the NJDEP has "failed in its mission ... failed or neglected to act in the best interest of the citizenry or has arbitrarily, capriciously or unreasonably acted." *Howell,* 207 N.J.Super. at 96, 504 A.2d 19; *Morris County Transfer Station, Inc. v. Frank's Sanitation Serv., Inc.,* 260 N.J.Super. 570, 578, 617 A.2d 291 (App.Div.1992) (permitting private ERA action where the NJDEP would not address violation for three years and had taken no enforcement actions against contaminating defendant who continued operating its illegal facility two months after receiving a violation notice). Where NJDEP "action subsequently proves sufficient to protect the environment," however, NJDEP "action under the Spill Act is preemptive of private rights under ERA." *Superior Air Prod.,* 216 N.J.Super. at 61, 522 A.2d 1025. The permissibility of private action must be evaluated on a case-by-case basis. *Id.*

Here the record indicates consistent and pervasive NJDEP oversight of the remediation process, requiring Defendant to regularly test Plaintiffs' wells and institute interim and permanent groundwater recovery systems. Plaintiffs have not claimed that the NJDEP failed to act or acted unreasonably, and there are no grounds for finding NJDEP inaction sufficient to permit a private ERA suit. Furthermore, as discussed below, Plaintiffs failed to give the NJDEP the requisite notice of their private suit. Accordingly, Defendant's motion for summary judgment of Plaintiffs' ERA claim will be granted.

2. Notice

***14** Before a private party may commence an action under the ERA, the party must "at least 30 days prior to the commencement thereof, direct a written notice of such intention by certified mail, to the Attorney General, the Department of Environmental Protection, the governing body of the municipality in which the alleged conduct has, or is likely to occur, and to the intended defendant." N.J.S.A. 2A:35A–11. The notice provision is intended to give the government an adequate opportunity to intervene in the litigation and to allow the NJDEP:

> to exercise value judgments in individual cases, e.g., whether it will join in that litigation or enforcement proceeding, whether other actions it may have taken already with respect to the particular problem or offender would render the litigation subject to collateral estoppel or res judicata principles, whether its expertise would assist the court, whether broad State interests would be sacrificed unduly to

> regional or personal interests by the instigators of that litigation, etc.

Howell, 504 A.2d at 95; *Morris County,* 260 N.J.Super. at 578, 617 A.2d 291 (quoting *Howell* for same).

Because Plaintiffs did not provide the required thirty day notice to the NJDEP or the Attorney General, they are barred from further pursuing their claim under the ERA. Plaintiffs argue that Defendant is judicially estopped from claiming lack of notice for failure to raise this issue at an earlier stage in the case. Plaintiffs analogize the ERA requirement to that of an affidavit of merit, required in certain cases to avoid "unmeritorious and frivolous malpractice lawsuits at an early stage of litigation." *Knorr v. Smeal,* 178 N.J. 169, 197–98, 836 A.2d 794 (2003) (holding judicially estopped defendant's request for summary judgment for plaintiff's failure to file affidavit of merit) (citing *Palanque v. Lambert–Woolley,* 168 N.J. 398, 404, 774 A.2d 501, 505 (2001)); *Ferreira v. Rancocas Orthopedic Assoc.,* 178 N.J. 144, 836 A.2d 779, (2003) (same).

Defendant argues that the ERA notice requirement is more analogous to the notice of intent in the Resource Conservation and Recovery Act (RCRA), which the Supreme Court held to be a jurisdictional prerequisite to suit in *Hallstrom v. Tillamook County,* 493 U.S. 20, 31, 110 S.Ct. 304, 107 L.Ed.2d 237 (1989) ("[C]ompliance with the 60–day notice provision is a mandatory, not optional, condition precedent for suit."); *Public Interest Research Group of N.J., Inc. v. Windall,* 51 F.3d 1179, 1189 (3d Cir.1995) (holding notice provision jurisdictional in context of Clean Water Act ("CWA")); *Hawksbill Sea Turtle v. Federal Emergency Mgmt. Agency,* 126 F.3d 461, 471 (3d Cir.1997) (holding notice provision jurisdictional in context of Endangered Species Act ("ESA")).

However, the language of the notice requirement in RCRA is not entirely analogous to that of the ERA. RCRA states, under the heading of "Actions prohibited" that "No action may be commenced ... prior to 60 days after the plaintiff has given notice of the violation to" the Administrator, the state and the alleged violator. 42 U.S.C.A. § 6972. The ERA lacks the "no action may be commenced" language of the RCRA, CWA, and ESA, and states only that notice must be sent "at least 30 days prior to the commencement" of suit. Consequently, the argument that the plain language of the statute creates a jurisdictional bar is not as strong in the context of the ERA.

***15** Nevertheless, because the purpose of the notice provision is to provide the Attorney General and NJDEP with notice of the suit and opportunity to intervene, *Howell,* 504 A.2d at 95, and not merely to protect defendants, as in the case of the affidavit of merit, Defendant is not judicially estopped from raising Plaintiffs' lack of compliance with the notice provision and is entitled to summary judgment of Plaintiffs' ERA claim.

E. Spill Act Claim

In their complaint, Plaintiffs assert a private right of action under the Spill Act, N.J.S.A. 58:10–23.11 *et seq.*[26] As amended in 1991, the Spill Act authorizes a private cause of action for individuals to recover costs for environmental damage to their property. *Housing Auth. of City of New Brunswick v. Suydam Inv., L.L.C.,* 177 N.J. 2, 18, 826 A.2d 673 (2003). Actions under the Spill Act are limited to clean up and removal costs, *Bahrle v. Exxon Corp.,* 145 N.J. 144, 155, 678 A.2d 225 (1996), defined as:

> all direct costs associated with a discharge, and those indirect costs that may be imposed by the department pursuant to section 1 of P.L.2002, c. 37 associated with a discharge, incurred by the State or its political subdivisions or their agents or any person with written approval from the department in the: (1) removal or attempted removal of hazardous substances, or (2) taking of reasonable measures to prevent or mitigate damage to the public health, safety, or welfare, including, but not limited to, public and private property.

N.J.S.A. 58:10–23.11b(d). The Act does not authorize "damages arising from emotional distress, enhanced risk of disease, loss of enjoyment of property, and other economic and financial harm." *Bahrle,* 145 N.J. at 155, 678 A.2d 225. Plaintiffs maintain that the investigation conducted by Ellwood was a reimbursable clean up and removal cost under the Spill Act. As Plaintiffs suggest, because "a discharge cannot be addressed until the contaminants are defined and the extent of the discharge determined," certain forms of investigative costs are implicitly included in the Act. *Metex Corp. v. Federal Ins. Co.,* 290 N.J.Super. 95, 115, 675 A.2d 220 (App.Div.1996).

However, for a private party to obtain reimbursement under the Act, the party must have obtained "written approval from the department," for example, in a memorandum of agreement, prior to incurring the cost. N.J.S.A. 58:10–23.11b(d); *Id.* Such approval permits the NJDEP to "review and approve or disapprove its investigation to date, its proposed remedial action, and its report of the implementation of its action." *Id.; see also* *Interfaith Cmty Org. v. Honeywell Intern., Inc.*, 263 F.Supp.2d 796, 867 (D.N.J.2003) (concluding "that such costs were approved by and/or incurred at the direction of NJDEP and thus are recoverable under the Spill Act."). Because Plaintiffs have not obtained NJDEP approval for any cost incurred, including the Ellwood report, Defendant is entitled to summary judgment of Plaintiffs' Spill Act Claim.

***16** The accompanying Order shall enter today.

Elcock, 233 F.3d at 741.

All Citations

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Footnotes

1 The following facts are taken from Defendant's statement of undisputed material facts, filed June 24, 2005, ("Undisputed Facts") and Plaintiffs' counterstatement of undisputed facts, filed Oct. 14, 2005, ("Counterstatement Facts"). Plaintiffs did not provide a separate statement of undisputed facts.

Although Plaintiffs dispute the majority of Defendant's statements of fact, Plaintiffs' counterstatements typically provide additional facts without setting forth any conflicting evidence. Where no actual disputes are presented, Defendant's statements will be treated as undisputed. *See e.g.,* *Tofano v. Reidel*, 61 F.Supp.2d 289, 292 n. 1 (D.N.J.1999) (citing Fed.R.Civ.P. 56(e)) ("This court will ... not consider assertions without evidential support as creating genuine issues of disputed fact."); *Talbot v. United States*, 2005 WL 2917463, *2 (D.N.J.2005) (noting that where the nonmoving party does not submit facts in opposition, "it is entirely appropriate for this court to treat all facts properly supported by the movant to be uncontroverted") (quoting *Allebach v. Sherrer*, No. 04–287, 2005 U.S. Dist. LEXIS 15626, at *5 (D.N.J.2005)).

More generally, Plaintiffs' brief suffers from numerous typographical errors and a dearth of citations to page numbers in the record. This "alone warrants exclusion of the evidence." *See* *Orr v. Bank of America, NT & SA*, 285 F.3d 764, 774–75 (9th Cir.2002) (holding that party's failure to cite page and line numbers when referencing the deposition merits exclusion of evidence); *Huey v. UPS, Inc.*, 165 F.3d 1084, 1085 (7th Cir.1999) ("[J]udges need not paw over the files without assistance from the parties."); *Nissho–Iwai Am. Corp. v. Kline*, 845 F.2d 1300, 1307 (5th Cir.1988) (parties must designate specific facts and their location in the record).

2 Among the original litigants to the suit were also former plaintiffs Michael and Susan Kammerhoff and Norma Simmons. The Kammerhoff plaintiffs were voluntarily dismissed, and plaintiff Norma Simmons died on August 26, 2000.

3 VOCs generally associated with gasoline discharge include MTBE, benzene, toluene, ethylbenzene, xylene (collectively "BTEX"), and tertiary butyl alcohol ("TBA"). The NJDEP has issued a Ground Water Quality Standard ("GWQS") for each of these VOCs, also known as "gasoline-related compounds." MTBE, for example, has a GWQS of 70 parts per billion ("ppb").

4 Although Motiva detected MTBE in thirteen residential wells, not all of these wells are owned by Plaintiffs to this litigation. Of the twenty-seven parcels of property at issue in this suit, only eight of the properties contain wells that ever tested positive for any gasoline-related compound.

5 The direction of water's flow in an aquifer is described as “downgradient,” and the direction against the current is “upgradient.”

6 In particular, testing revealed emissions in monitoring wells 6–Shallow (“MW–6S”) and 7–Deep (“MW–7D”), which lie between the Motiva site and the residential properties. However, the majority of upgradient monitoring wells did not test positive for gasoline-related contaminants. (NJDEP Directive, March 21, 2001 (“March 2001 Directive”), Mairo Cert. in Supp. Def.'s Mot. Summ. J., filed June 24, 2005 (“Mairo Cert.”), Ex. O, at 4.)

7 Plaintiffs dispute Defendant's characterization of the CEA, (Counterstatement Facts ¶ 31), on the basis that Defendant proposed the CEA prior to conducting an actual delineation of the plume and that “the Plaintiffs' residential wells could only had [sic] been included in the CEA, if Defendant intended to supply a permanent public water supply to Plaintiffs' properties.” While Plaintiffs' contention with the CEA is not entirely clear, Plaintiffs have not provided any evidence indicating that the NJDEP improperly approved the CEA or that the CEA was an inaccurate representation of the boundaries of contaminants in excess of the GWQS.

8 Plaintiffs' properties are: 850 Sicklerville Road; 565, 569, 581, and 583 Berlin–Cross Keys Road; 6, 9, 10, 12, 13, 14, 1, 16, 17, 18, 20 Spring Hollow; 2, 4, 6, and 8 Latham Way; 3, 4, 5, 7, 12, 14, and 15 Donna Marie Court.

9 CW–8 is located approximately 1,000 feet downgradient of the contamination site. (March 2001 Directive at 2.) While active, CW–8 pumps approximately 500 gallons per minute and causes the groundwater to flow southwest. (Ellwood Report at 2.) When CW–8 is not pumping, the groundwater flow is more westerly. (Ellwood Report at 2.)

10 Plaintiff disputes these facts on the basis that:

> The Defendant has no data for any portable [sic] water supply of the Plaintiffs prior to July 2000. The Defendant never performed any delineation of the groundwater plume in the areas of the residential properties despite having actual knowledge of such contamination in MW–6, MW–7 and MW–12. See Gallo Certification and Exhibits C, D and E.

(Counterstatement Facts ¶¶ 46–48.) However, because Defendant makes no averment of the presence or absence of contamination prior to July 2000, Defendant's statements are not actually in dispute. Plaintiffs provide no fact indicating an inaccuracy in Defendant's statements regarding the testing of Plaintiffs' wells. Consequently, there is no actual dispute regarding the presence or amount of *detected* gasoline-related compounds.

11 Plaintiffs dispute these statements by citing to Exhibit F of the McKenna certification; however, Exhibit F is the Ellwood report and therefore is not indicative of the NJDEP requirements. Plaintiffs nowhere cite to a statement by the NJDEP requiring Defendant to treat their water or provide them with an alternate water source, and therefore this fact is undisputed.

12 Because this Court will grant Defendant's motion for summary judgment, it will not reach the merits of Defendant's motions to exclude experts Gochfeld, Ellwood, and Gallo.

13 After *Daubert,* Rule 702 was amended to encompass the *Daubert* analysis:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed.R.Evid. 702. While *Daubert* itself addressed only the admissibility of scientific evidence, the Court has since noted that courts' gatekeeping obligations extend to all expert testimony. *Kumho Tire Co. v. Carmichael,* 526 U.S. 137, 151, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999).

14 The Court noted that it had “misgivings” about the expert's qualifications in spite of:

> (1) [the expert's] general training in “assessing” individuals, which he received while earning his Ph.D. in psychology; (2) his experience, twenty years previous, helping drug addicts reenter the workforce; (3) his experience primarily in the last two years dealing with the Virgin Islands Division of Workers' Compensation, which he had advised regarding the ability of approximately fifty to sixty-five disabled employees to return to their previous jobs; (4) his past experience as an expert witness making lost earning capacity assessments; (5) his attendance at two seminars regarding vocational rehabilitation, and his stated familiarity with the literature in the area; (6) his membership in two vocational rehabilitation organizations, both of which place no restrictions on membership; and (7) the fact that when [the expert] was in school, a degree in vocational rehabilitation therapy was not available, but that he received similar training nonetheless.

15 Plaintiffs also argue that “Defendant does not attack the methodology, standard or factual basis for the opinions,” (Opp. at 31), however, it is quite clear from Defendant's motion that the reliability of McDonald's methodology is hotly disputed.

16 McDonald also appeared unaware of the fact that Plaintiffs' properties are served by potable wells, even though the potable wells contain the evidence of contamination.

> Q: Do you know whether or not the plaintiffs' properties have potable wells?
>
> A: It's my understanding that they are hooked to a public water system.
>
> Q: If each of the properties did in fact have a potable well, would that be a factor that you were consider relevant in your analysis?
>
> Mr. McKenna: You may want to review the documents that you referenced in your report to assist you in this area. Just separate the Ellwood and Gallo reports. I'm going to go to the men's room.
>
> (Whereupon, a recess is taken.)
>
> Mr. Mairo: I am going to object that Mr. McKenna was basically coaching the witness.
>
> Back on the record.
>
> A: Your question about whether or not each of these houses were, was, had their own private well on site-
>
> Q: Uh-huh?
>
> A: -it's my understanding that each house is served by wells within and around the neighborhood and that Consumer, Consumers Water Company owns those wells and supplies that water to the homes.

(McDonald Dep. at 36.)

17 McDonald reaches the 35% devaluation figure with the following methodology:

> The subject properties are in the early stages of monitoring, and clean up of the ground water contamination. The properties from Dover Twp. are beyond the clean up stage and into the final stage of recovery, yet they still show a 13% loss in value as compared to similar properties outside of the contaminated area. The subject area is in stage D of recovery, which is the beginning of the remediation process. Based on the acceptance of the Detrimental Condition Model as a viable process for valuing Detrimental Conditions to Real Estate, by the appraisal community and the Subcommittee on Housing and Community Opportunity of the House Committee on Financial Services, it would be logical to assume that the discount to the properties which are the subject of this report, would be 2 to 3 times that of properties in the final stage of recovery. In this case a discount of 35% would be considered reasonable.

(McDonald Report at 31.)

18 Interbay Funding, for example, qualified their statement that they would not lend by noting, “The property would have to be completely cleaned up. They would have to file all necessary documents to the state of NJ and we would require something from the state telling us the property is cleaned up.” (McDonald Report at 32.) From this, McDonald concluded that Interbay Funding would not lend on properties such as Plaintiffs', without considering that none of Plaintiffs' properties were contaminated in excess of state standards.

19 In evaluating this data, McDonald states:

> The lenders that did respond have overwhelmingly stated that they would not approve the loan at all, or they would require substantial conditions to the loan. In the case of the subject properties, it can be assumed that a purchaser with private financing or cash would be the only potential buyer of houses in this area.

(McDonald Report at 32.)

20 Because the Court now finds that there is no evidence of any actual injury arising from Defendant's negligence, this Court will not address Defendant's causation argument.

21 Plaintiff argues that Defendant's motion for summary judgment of its negligence claim should be denied on the basis of the doctrine of *res ipsa loquitur.* However, *res ipsa loquitur* acts only to “permit[ ] an inference of defendant's negligence” (i.e., that defendant acted in an unreasonable manner) under particular circumstances. *Jerista v. Murray,* 185 N.J. 175, 192, 883 A.2d 350 (2005). The doctrine does not establish either causation or the presence of damages. *See e.g., Bahrle v. Exxon Corp.,* 279 N.J.Super. 5, 35, 652 A.2d 178 (App.Div.1995) (holding *res ipsa* doctrine inapplicable where “there was a factual dispute as to whether the contamination was a result of plaintiffs' own voluntary acts or neglect”). Accordingly, because Defendant is contesting only causation and damages, the *res ipsa* doctrine does not apply.

22 Gochfeld testifies in his deposition that he created his report without any specific information about the Plaintiffs:

> Q: So, for example, in determining the percentage of the target population that was in high exposure category, that wasn't based on the ground water, your review of the ground water tables that were attached to Mr. Gallo's report?
>
> A: It was not.

Q: That was based purely on just an assumption of yours?

A: It was an assumption based on experience with previous programs or programs that are currently underway in our communities.

Q: Having no specific factual knowledge of the actual exposures in this case?

A: That's correct, these are hypotheticals.

(Gochfeld Dep. at 28–29.)

23 Gochfeld also states that he would not even recommend medical monitoring for the one property with by far the highest detection of MTBE (13.8 ppb at 4 Latham Way) "on this data alone" because "[i]t is possible that a person living there would only be drinking bottled water, would not be in the house very much." (Gochfeld Dep. at 50.)

24 Defendant argues further that New Jersey law does not permit Plaintiffs to recover for stigma damages in the absence of some physical harm to their property. Because Plaintiffs have provided no evidence of any stigma to their property, the Court will not reach Defendant's alternative argument.

25 It is unclear whether Plaintiffs allege negligent trespass since they discuss only the Restatement (Second) of Torts § 158, Intentional Trespass, in their Opposition. Unlike intentional trespass, negligent or reckless trespass requires evidence of "harm to the land, to the possessor, or to a thing or a third person." Rest. Torts 2d § 165; *see also* *Burke v. Briggs,* 239 N.J.Super. 269, 271, 571 A.2d 296 (App.Div.1990) (citing Rest.2d Torts § 158 with approval for another premise); *Karpiak v. Russo,* 450 Pa.Super. 471, 481, 676 A.2d 270 (Pa.Super.1996) (affirming dismissal of trespass claim for entry of dust onto property since the "evidence failed to establish that the dust caused appellants harm"). As discussed previously, Plaintiffs have not provided any evidence of injury to their persons or property. Consequently, to the extent that Plaintiffs are claiming negligent trespass, Defendant is entitled to summary judgment.

26 It is unclear whether Plaintiffs also raise a claim for cleanup and removal costs from the Spill Compensation Fund under N.J.S.A. 58:10–23.11g(a). (Opp. at 12–13.) However, the appropriate procedure to obtain compensation under the Fund is by filing a claim with the administrator of the Fund, "not later than one year after the date of discovery of damage. The administrator shall prescribe appropriate forms and procedures for such claims." N.J.S.A. 58:10–23.11k. In the event "a party, including a potentially responsible party ... contests the amount or validity of" a claim for reimbursement from the Spill Fund, "the dispute is referred to an arbitrator whose decision may be appealed to the Appellate Division," and the arbitrator's decision will be final unless it was "arbitrary, capricious, or unreasonable." *Lacey Municipal Util. Auth. v. New Jersey Dept. of Envir. Prot., Envir. Claims Admin.,* 369 N.J.Super. 261, 273, 848 A.2d 843 (App.Div.2004). Accordingly, this is an improper forum for a Spill Compensation Fund claim.

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